HOW IS THE NEW KIDNEY ALLOCATION SYSTEM WORKING? INSIGHTS FROM HIGHLY SENSITIZED AND PEDIATRIC PATIENTS

by
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ABSTRACT

The Kidney Allocation System (KAS) was implemented on December 4, 2014, and was the largest policy change to how deceased donor kidneys are allocated in the United States in the last two decades. Since policy change can have unintended consequences, we sought to critically examine how KAS has impacted kidney transplant candidates and recipients. This dissertation focuses on two unique transplant populations: highly sensitized (HS, calculated panel reactive antibody [cPRA] ≥80%) and pediatric (age <18) patients.

First, one explicit goal of KAS was to improve the likelihood that a HS kidney transplant candidate would receive a deceased donor kidney transplant (DDKT), and we sought to quantify the extent to which KAS accomplished this goal (Chapter 2). Using national data, we found that candidates with the highest levels of sensitization had a significantly higher DDKT rate post-KAS (for example, cPRA 98% candidates had a 1.77-fold higher DDKT rate). We then sought to understand how other transplant modalities were being used to transplant the HS (Chapter 3). We used national data from 39,907 HS candidates and found that HS candidates were 2.25-fold more likely to utilize kidney paired donation but 18% less likely to utilize non-kidney paired donation living donor kidney transplantation in the post-KAS era compared to earlier eras.

We then studied how KAS impacted pediatric DDKT recipient outcomes, in light of concerns that fewer pediatric donor kidneys were being allocated to pediatric DDKT recipients (Chapter 4). We used national data from 1,887 pediatric DDKT candidates and found that post-KAS pediatric DDKT recipients had a 41% lower risk of graft loss than pre-KAS recipients. We then studied changes in offer and acceptance patterns under KAS (Chapter 5). Using national data from 3,642 pediatric DDKT candidates, we found that post-KAS candidates were 20% more likely to receive offers from donors age 18-34 with KDPI ≤35%, but were also 23% less likely to accept kidneys from those same high-quality donors.

Our results will be used by pediatric and adult nephrologists, transplant surgeons, and policy-makers to understand how KAS has impacted HS and pediatric candidates and recipients to better inform any potential policy changes.

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Chapter 1. Introduction

The Kidney Allocation System (KAS) was implemented on December 4, 2014, and was the largest policy change to how deceased donor kidneys are allocated to kidney transplant candidates in the United States in last two decades.[1] KAS was designed after an Organ Procurement and Transplantation Network (OPTN) mandate to revise the prior allocation system that was predominantly driven by waiting time, instead of medical criteria.[2, 3] The primary goals of KAS were to increase equity in allocation by eliminating disparities in access to transplantation for the highly sensitized (HS) and certain racial minorities, to increase utility in allocation through matching the highest-quality kidneys to recipients expected to live the longest post-transplant ("longevity matching"), and to reduce kidney discard.[1, 3, 4]

One explicit goal of KAS was to improve deceased donor kidney transplant (DDKT) rates for the HS. The degree of sensitization for a particular candidate is measured as calculated panel reactive antibody (cPRA), which represents the percent of deceased donors to which that candidate is incompatible with (and cannot receive a transplant from).[5] Prior to KAS, every transplant candidate with a cPRA ≥80% was awarded the same allocation priority, even though a candidate's likelihood of DDKT varies substantially as cPRA approaches 100%.[6] For example, a cPRA 80% candidate would only require 14 match runs to have a 95% probability of finding a compatible donor, whereas a cPRA 99.9% candidate would require 3,000 match runs. KAS was designed to ameliorate this discrepancy by instituting a sliding scale for priority points, where more points were awarded the higher the cPRA.[1] Although early simulations suggested that this change would minimize differences in DDKT rates based on cPRA, changes to allocation policy can often result in unintended consequences.[7-9]

Early reports on the impact of KAS found that DDKT rates increased for cPRA ≥98% candidates.[10-14] In one of these studies, the percentage of DDKT recipients with cPRA ≥99% increased 5.4-fold in

the first year after KAS.[14] Additionally, there was evidence that this initial increase in DDKT rates for cPRA 100% candidates might be a 'bolus effect', whereby a large number of these candidates got transplanted in the first few months after KAS, and the 'steady state' DDKT rate was lower.[14] However, these studies focused largely on cPRA ≥98% candidates, even though KAS directly modified the allocation priority points that other HS DDKT candidates receive. Moreover, these studies did not quantify how HS candidate's utilization of other transplant modalities, such as living donor kidney transplantation or kidney-paired donation (where two incompatible donor/recipient pairs 'swap' donors to receive a compatible living donor transplant). Since choosing the transplant strategy associated with the highest long-term survival depends highly on the likelihood of all transplant modalities, it is critical to understand current 'steady-state' DDKT rates for all HS candidates under KAS, as well as the likelihood of other transplant modalities such as kidney-paired donation and living donor kidney transplantation.

Although pediatric candidates were not the direct focus of KAS, every effort was made to ensure that they retained the 'pediatric advantage' – that is, the relatively high priority pediatric candidates received for high-quality donor kidneys under the prior allocation system, given that they have the longest expected life with the transplant. Prior to KAS, pediatric candidates were allocated kidneys from donors <35 years old, whereas under KAS they are allocated kidneys from donors with a Kidney Donor Profile Index (KDPI) <35%.[1] KDPI represents the relative quality of a donor kidney compared to other donor kidneys from the year prior, so a KDPI 35% would mean that donor kidney would have a predicted graft lifespan longer than 35% of all donor kidneys recovered the year prior. Although this change from prioritization based on age to KPDI did not directly modify pediatric candidates place on the allocation sequence, KAS did lead to HS candidates receiving higher allocation priority than pediatric candidates.

There have been a number of unintended changes for pediatric candidates under KAS. One of these unintended changes has been a 21% decrease in DDKT rates for candidates <6 years old.[15] Also, two studies have described a decrease in the number of pediatric recipients receiving organs from pediatric donors, with absolute decreases ranging from 3.3% - 11%.[16, 17] One other study found a 121 day increase in the amount of time recipients <10 years old spent on the waitlist prior to transplant post-KAS, and an absolute 6.7% increase in the percentage of recipients waiting longer than one year for transplant.[17] These changes under KAS have led to concerns that KAS violates the ethical principles of utility (pediatric recipients are less frequently receiving high-quality kidneys from pediatric donors) and justice (decreased likelihood of DDKT for pediatric candidates < 6 years old), and some have proposed modifications to KAS to attempt to reverse these changes.[18, 19] To better inform any potential policy change, it would be useful to understand how KAS has impacted post-DDKT outcomes for pediatric recipients, as well as altered the types (and quality) of donor kidneys being allocated to pediatric candidates.

This dissertation focuses on how KAS impacted HS and pediatric candidates and recipients. In Chapter 2, DDKT rates for HS candidates are compared before and after KAS using national registry data. In Chapter 3, temporal trends in kidney-paired donation and living donor kidney transplantation rates for HS candidates are quantified using national registry data. In Chapter 4, post-DDKT outcomes for pediatric recipients before and after KAS are compared using national registry data. Finally, in Chapter 5, deceased donor kidney offer and acceptance patterns for pediatric candidates are compared before and after KAS using national registry data. We hypothesized that DDKT rates would increase for the HS post-KAS, and that KAS would lead to a different spectrum of kidney offers to pediatric candidates, although acceptance would remain unchanged.

Chapter 2. The National Landscape of Deceased Donor Kidney Transplantation for the Highly Sensitized: Transplant Rates, Waitlist Mortality, and Post-Transplant Survival Under KAS

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ABSTRACT

Deceased donor kidney transplantation (DDKT) rates for highly sensitized (HS) candidates increased early after implementation of the Kidney Allocation System (KAS) in 2014. However, this may represent a bolus effect, and a granular investigation of the current state of DDKT for HS candidates remains lacking. We studied 270,722 DDKT candidates from the SRTR from 12/4/2011–12/3/2014 ('pre-KAS') and 12/4/2014–12/3/2017 ('post-KAS'), analyzing DDKT rates for HS candidates using adjusted negative binomial regression. Post-KAS, candidates with the highest levels of sensitization had an increased DDKT rate compared to pre-KAS (cPRA 98% adjusted incidence rate ratio [aIRR]:$_{1.27}1.77_{2.46}$ p=0.001, cPRA 99% aIRR:$_{3.18}4.36_{5.98}$ p<0.001, cPRA 99.5-99.9% aIRR:$_{16.91}24.29_{34.89}$ p<0.001, and cPRA 99.9%+ aIRR:$_{8.79}11.58_{15.26}$ p<0.001). To determine whether these changes produced more equitable access to DDKT, we compared DDKT rates of HS to non-HS candidates (cPRA 0-79%). Post-KAS, cPRA 98% candidates had an equivalent DDKT rate (aIRR:$_{0.65}0.94_{1.36}$, p=0.8) to non-HS candidates, whereas 99% candidates had a higher DDKT rate (aIRR:$_{1.19}1.68_{2.38}$, p=0.02). Although cPRA 99.5-99.9% candidates had an increased DDKT rate (aIRR:$_{2.46}3.50_{4.98}$, p<0.001) compared to non-HS candidates, cPRA 99.9%+ candidates had a significantly lower DDKT rate (aIRR:$_{0.29}0.40_{0.56}$, p<0.001). KAS has improved access to DDKT for HS candidates, although substantial imbalance exists between cPRA 99.5-99.9% and 99.9%+ candidates.

INTRODUCTION

The deceased donor kidney allocation algorithm underwent a major revision in December 2014 with the implementation of the new Kidney Allocation System (KAS). One of the goals of KAS was to improve access to deceased donor kidney transplantation (DDKT) for highly sensitized (HS) candidates.[1] Compared to non-HS candidates, HS candidates had as much as a five-fold lower rate of DDKT and 21% higher waitlist mortality prior to KAS.[20-22] KAS was designed to ameliorate these differences by awarding extra allocation points based on calculated panel-reactive antibody (cPRA) and by implementing local, regional, and national sharing for those with a cPRA ≥ 98%.[1] Simulations prior to KAS implementation suggested that these measures would increase DDKT rates for HS candidates by varying amounts based on cPRA, such that DDKT recipients with a cPRA 100% would increase by as much as three-fold.[7]

Since the implementation of KAS, several studies have shown an early increase in DDKT rates for HS candidates.[10-14] In one study, the percentage of DDKT recipients with a cPRA ≥ 99% increased 5.4-fold in the first year of KAS.[13] However, none of these studies examined changes in DDKT rates beyond one year after KAS implementation. Our group has shown that this early increase in DDKT rates for patients with cPRA 100% may represent a "bolus effect", such that 12% of DDKT recipients had a cPRA 100% in the first month of KAS, but this had decreased to 7% by the ninth month after KAS.[14] Moreover, prior studies have generally focused on patients with a cPRA ≥ 98%, even though KAS directly modified the allocation points received by other HS kidney transplant candidates as well.[1] Since the relative benefit of DDKT compared to other potentially available transplant options for HS candidates, such as kidney-paired donation or incompatible living donor kidney transplantation, depends highly on the likelihood of DDKT, an understanding of current DDKT rates under KAS is critical to determining the optimal transplant approach for a given patient.[23, 24]

To understand the current state of DDKT for HS candidates, we analyzed national waitlist data. The goals of our study were to: (i) to compare long-term DDKT rates for HS candidates before and after KAS, (ii) to compare DDKT rates of HS candidates to non-HS candidates after KAS, (iii) to determine the cumulative incidence of DDKT and waitlist mortality for HS candidates beyond the first year after KAS implementation, and (iv) to determine whether post-transplant outcomes for HS recipients have changed after KAS.

METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[25] The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study Population

We studied all prevalent adult (age ≥ 18 years) kidney-only waitlist candidates and DDKT recipients from December 4, 2011 to December 3, 2017. For waitlisted candidates, only active patient time was included for analysis. This study was approved by the Johns Hopkins Medicine Institutions Institutional Review Board.

Time Periods for Analysis

Our study period was divided into two major time periods: pre-KAS (12/4/2011 to 12/3/2014) and post-KAS (12/4/2014 to 12/3/2017). To isolate a possible bolus effect, we further divided the post-KAS time period into successive six-month intervals.

cPRA Categories for Analysis

A candidate's cPRA was obtained from SRTR's cPRA history dataset, which has every cPRA value reported. As such, for patients whose cPRA changed while on the waitlist, the time they spent at each cPRA contributed patient-time to that cPRA category when calculating DDKT rates.

We divided HS waitlist candidates into the following cPRA categories: 80-89%, 90-97%, 98%, 99%, 99.5-99.9%, and 99.9%+. These categories were chosen to allow for similar allocation priority between candidates within a cPRA group while also including enough candidates in each group to allow for well-powered comparisons. For example, cPRA 80% candidates receive 2.46 points under KAS, and cPRA 89% candidates receive 4.05 points. This range of allocation points is small enough such that differences in allocation priority should be minimal. Conversely, a much larger range in allocation points is provided to cPRA 98% (24.4 points), 99% (50.1 points), and 100% (202.1 points), and these candidates receive different organ sharing priority (local sharing for cPRA 98%, regional sharing for cPRA 99%, and national sharing for cPRA 100%), so we chose to analyze them separately. Since cPRA 100% candidates may have different DDKT rates depending on their unrounded cPRA, we further divided these candidates into 99.5-99.9% and 99.9%+ categories.

DDKT Rates for HS Candidates After KAS Compared to Before KAS

We used an adjusted negative binomial regression model to estimate the relative DDKT rate within each cPRA category for each of the post-KAS time periods relative to pre-KAS. We used a sandwich estimator to account for within-organ procurement organization (OPO) clustering of DDKT rates.[26] We adjusted this model for covariates also known to affect DDKT rate (e.g. candidate age, ABO blood type, race, gender, and time on dialysis). We included an interaction term between KAS and cPRA group to allow the effect of KAS to vary across different cPRA groups. To study a potential bolus effect, we then tested for overall trends in DDKT rates post-KAS for each cPRA category.

DDKT rates for HS candidates compared to non-HS candidates

In order to determine whether DDKT rates for HS candidates had become more equitable compared to non-HS candidates following KAS, we used the adjusted negative binomial regression model to compare DDKT rates between each HS candidate group and the non-HS group (cPRA 0-79%). In doing so, we were able to determine whether the post-KAS changes to DDKT rates within a given cPRA group led to overall more balanced DDKT rates between all cPRA groups.

Cumulative incidence of DDKT and waitlist mortality after KAS for specifc cPRA groups

To estimate time to DDKT post-KAS, we modeled the cumulative incidence of DDKT for each cPRA group. To do this, we constructed a proportional hazards model under a competing risk framework using the Fine and Gray method.[27] Receipt of DDKT was the outcome of interest, with a competing risk of death or removal from the waiting list due to deteriorating clinical status. Patients who were removed from the waiting list for any other reason (such as receipt of a living donor transplant) were censored. We modeled the cumulative incidence of waitlist mortality similarly, where death while on the waitlist was the outcome of interest, with a competing risk of DDKT. As the goal of this analysis was to determine intention-to-treat time to DDKT (or waitlist mortality) based on

cPRA, accounting for competing risks, we included both active and inactive waitlist time in these models. Under the competing risks framework, we were also able to model adjusted subhazard ratios within the subdistribution of the outcome of interest (either DDKT or waitlist mortality), with the other outcome as a competing event.

Post-transplant patient and graft survival after KAS

Post-transplant patient survival and death-censored graft survival (DCGF) for DDKT recipients pre-KAS and post-KAS were compared using Kaplan-Meier methodology and Cox proportional hazards regression, adjusting for candidate age, ABO blood type, race, gender, and time on dialysis. We included an interaction term between KAS and cPRA group to allow the effect of KAS to vary across different cPRA groups.

Statistical analysis

To compare baseline characteristics between DDKT recipients before and after KAS, we used the chi-squared test for categorical variables, student's t-test for normally-distributed continuous variables, and the Kruskal-Wallis test for non-normally distributed continuous variables. A two-tailed p-value of <0.05 was considered statistically significant. Confidence intervals are reported as per the method of Louis and Zeger [28]. Statistical analysis was performed using Stata 15.0 (StataCorp, College Station, TX).

RESULTS

Study Population

We identified 270,722 waitlisted candidates from December 4, 2011 to December 3, 2017. Of these, 30,031 were transplanted pre-KAS and 35,172 were transplanted post-KAS. Compared to pre-KAS recipients, post-KAS recipients were younger (52.4 years vs. 53.9, p<0.001), more likely to be female (39.3% vs. 40.4%, p=0.003), and more likely to be black (35.5% vs. 32.2%, p<0.001) (Table 1). ABO blood type was not significantly different between post-KAS and pre-KAS recipients. Post-KAS recipients were significantly more likely to have a cPRA of 100% compared to pre-KAS recipients (8.1% vs. 1.1%, p<0.001), more likely to have had a prior kidney transplant (14.7% vs. 13.0%, p<0.001), have spent more time on dialysis prior to DDKT (4.6 years vs. 2.3, p<0.001), have a slightly lower estimated post-transplant survival score (45.8 vs. 46.4, p=0.002), and have received a donor kidney that had been shared nationally (17.9% vs. 13.4%, p<0.001). Post-KAS, cPRA 99.9%+ candidates were the most common group of HS candidates on the waitlist (Figure 1). No group of HS candidates represented more than 5% of candidates on the waitlist.

DDKT Rates for HS Candidates Before and After KAS

DDKT rates were dramatically increased post-KAS compared to pre-KAS for both cPRA 99.5-99.9% candidates (adjusted incidence rate ratio [aIRR] of DDKT at 3 years post-KAS: $_{16.91}24.29_{34.89}$, p < 0.001) and cPRA 99.9%+ candidates (aIRR: $_{8.79}11.58_{15.26}$, p<0.001) (Table 2, Figure 2). There was no evidence of a bolus effect for either group (p=0.4, p=0.1, respectively). Similar, albeit lower, increases were seen for patients with a cPRA of 99% (aIRR: $_{3.18}4.36_{5.98}$, p<0.001) and a cPRA of 98% (aIRR: $_{1.27}1.77_{2.46}$, p=0.001), also with no evidence of a bolus effect.

However, not all groups of HS candidates benefited from KAS. Notably, cPRA 80-89% candidates experienced a significant decline in DDKT rates in the first 6 months following KAS (aIRR: $_{0.19}0.24_{0.30}$, p<0.001). While this decrease in DDKT rates improved over time (p<0.001), DDKT rates at three years post-KAS remained significantly lower compared to pre-KAS (aIRR: $_{0.35}0.45_{0.58}$, p<0.001). Similarly, cPRA 90-97% candidates experienced a significant decline in DDKT rates in the

first 6 months post-KAS (aIRR: $_{0.53}0.65_{0.81}$, p<0.001), but by three years post-KAS their DDKT rate was again equivalent to their pre-KAS rate (aIRR: $_{0.97}1.26_{1.64}$, p=0.1).

DDKT Rates for HS Candidates Compared to non-HS Candidates

For most cPRA ranges, the wide differences in DDKT rates between cPRA categories pre-KAS became less pronounced post-KAS (Table 3, Figure 3). However, there was significant heterogeneity in DDKT rates for cPRA 100% candidates. For example, cPRA 99.9%+ candidates were transplanted at a 97% lower rate than non-HS candidates pre-KAS (aIRR: $_{0.02}0.03_{0.04}$, p<0.001), but continued to be transplanted at a lower, albeit improved, rate at three years post-KAS (aIRR: $_{0.29}0.40_{0.56}$, p<0.001). Conversely, cPRA 99.5-99.9% candidates were transplanted at a 88% lower rate than non-HS candidates pre-KAS (aIRR: $_{0.10}0.12_{0.15}$, p<0.001), but were transplanted at a substantially higher rate three years post-KAS (aIRR: $_{2.46}3.50_{4.98}$, p<0.001)

cPRA 99% candidates had a notably lower DDKT rate than non-HS candidates pre-KAS (aIRR $_{0.24}0.29_{0.35}$, p<0.001), but were transplanted at a higher rate three years post-KAS (aIRR: $_{1.19}1.68_{2.38}$, p=0.02). cPRA 98% candidates were transplanted at a 56% lower rate than non-HS candidates pre-KAS (aIRR: $_{0.35}0.44_{0.55}$, p<0.001), but improved to equivalent DDKT rates three years post-KAS (aIRR: $_{0.65}0.94_{1.36}$, p=0.8). Although cPRA 80-89% patients experienced a significant decrease in DDKT rates post-KAS compared to pre-KAS, these patients continued to have a higher DDKT rate than non-HS candidates both pre-KAS (aIRR $_{2.69}3.27_{3.97}$, p<0.001) and post-KAS (aIRR: $_{1.50}1.79_{2.14}$, p<0.001). Thus, their decline in DDKT rates post-KAS does not appear to have disadvantaged them compared to other transplant candidates.

Cumulative incidence of DDKT based on cPRA

The range of likelihood of DDKT at 1-year for a given cPRA category was smaller post-KAS (range 9.4-32.9%) then pre-KAS (range 1.4 - 28.1%) (Figure 4). For example, a cPRA 99.5-99.9% candidate

had a 1-year cumulative incidence of DDKT of 3.9% pre-KAS, but post-KAS this improved to 32.9%. In comparison, a cPRA 99.9%+ candidate had a 1-year cumulative incidence of DDKT of 1.4% pre-KAS, but post-KAS this improved to 9.4%. Notably, the highest and lowest cumulative incidence of DDKT post-KAS were in cPRA 99.5-99.9% (32.9%) and cPRA 99.9%+ candidates (9.4%), respectively. The 1-year cumulative incidence of DDKT post-KAS for cPRA 99% (26.2%), 98% (19.4%), 90-97% (21.7%), 80-89% (19.3%), and 0-79% (14.0%) candidates were broadly similar (Table 4). Similar patterns extended to three years post-KAS, where the highest and lowest cumulative incidence of DDKT post-KAS were in cPRA 99.5-99.9% (48.4%) and cPRA 99.9%+ candidates (20.2%), respectively. The range of the cumulative incidence of DDKT continued to be smaller three years post-KAS (20.2 - 48.4%) compared to pre-KAS (4.2 - 44.4%). No group of candidates had a median time to DDKT of less than 3 years.

Post-KAS, most HS candidates had an increased likelihood of DDKT relative to non-HS candidates, after accounting for the competing risk of waitlist mortality or removal from waitlist due to deteriorating medical condition (Table 6). cPRA 80-89% (adjusted subhazard ratio [aSHR]: $_{1.19}1.34_{1.51}$, $p<0.001$), 90-97% (aSHR: $_{1.24}1.48_{1.77}$, $p<0.001$), 98% (aSHR: $_{1.14}1.37_{1.64}$, $p=0.001$), 99% (aSHR: $_{1.42}1.73_{2.10}$, $p<0.001$), and 99.5-99.9% (aSHR: $_{1.74}2.08_{2.47}$, $p<0.001$) candidates were all more likely to undergo DDKT than non-HS candidates. Conversely, cPRA 99.9%+ candidates were less likely to undergo DDKT than non-HS candidates (aSHR: $_{0.49}0.60_{0.75}$, $p<0.001$)

Cumulative incidence of waitlist mortality based on cPRA

The range of likelihood of waitlist mortality at-year for a given cPRA category was similar post-KAS (range 4.7-7.4%) and pre-KAS (3.7-6.1%) (Figure 5). The 1-year cumulative incidence of waitlist mortality post-KAS for cPRA 99.9%+ (7.4%), 99.5-99.9% (6.1%), 99% (5.8%), 98% (6.0%), 90-97% (5.0%), 80-89% (4.7%), and 0-79% (5.0%) candidates were broadly similar. (Table 5). Similar patterns

extended to three years post-KAS, where the range of three year cumulative incidence of waitlist mortality was similar post-KAS (15.9-21.8%) and pre-KAS (12.8-21.3%).

After adjusting for candidate characteristics, many HS candidates continued to have a slightly higher likelihood of waitlist mortality relative to non-HS candidates post-KAS, accounting for their competing risk of DDKT (Table 6). cPRA 98% (aSHR: $_{1.16}1.44_{1.80}$, p=0.001), 99% (aSHR: $_{1.06}1.27_{1.52}$, p=0.01), 99.5-99.9% (aSHR: $_{1.19}1.44_{1.74}$, p<0.001), and 99.9%+ candidates (aSHR: $_{1.59}1.89_{2.25}$, p<0.001) all had a higher likelihood of waitlist mortality relative to non-HS candidates.

Post-transplant patient and death-censored graft survival based on cPRA

One-year post-transplant patient survival was similar for HS candidates post-KAS and pre-KAS (96.6% and 97.2% for cPRA 80-89% candidates, 96.6% and 97.3% for cPRA 90-97% candidates, 97.6% and 97.2% for cPRA 98% candidates, 96.4% and 96.9% for cPRA 99% candidates, 96.9% and 97.0% for cPRA 99.5-99.9% candidates, and 96.0% and 97.0% for cPRA 99.9%+ candidates, respectively). After adjusting for recipient characteristics, there were no differences in one-year post-transplant mortality for HS candidates post-KAS compared to pre-KAS (Table 7).

One-year post-transplant death-censored graft survival was higher for HS candidates post-KAS compared to pre-KAS (97.4% and 96.3% for cPRA 80-89% candidates, 97.6% and 94.5% for cPRA 90-97% candidates, 98.8% and 92.7% for cPRA 98% candidates, 97.9% and 94.4% for cPRA 99% candidates, 96.8% and 95.6% for cPRA 99.5-99.9% candidates, and 96.6% and 95.0% for cPRA 99.9%+ candidates, respectively, p<0.001). After adjusting for recipient characteristics, only cPRA 90-97% (adjusted HR [aHR]: $_{0.29}0.43_{0.62}$, p<0.001), cPRA 98% (aHR: $_{0.1}10.26_{0.63}$, p=0.003), and cPRA 99% candidates (aHR: $_{0.17}0.36_{0.77}$, p=0.008) had a decreased risk of one-year death-censored graft failure post-KAS compared to pre-KAS (Table 7).

DISCUSSION

In this nationwide study examining DDKT rates for HS candidates after KAS, we found no bolus effect and that DDKT rates for HS candidates continued to be dramatically different even 3 years after implementation of KAS. The large disparities in DDKT rates that existed prior to KAS across cPRA levels were substantially reduced at 3-years post-KAS. However, there continue to be large differences in DDKT rates for groups of cPRA 100% candidates, with cPRA 99.5-99.9% candidates having a significantly higher DDKT rate (aIRR: $_{2.46}3.50_{4.98}$) compared to non-HS candidates. Conversely, cPRA 99.9%+ candidates had a substantially lower DDKT rate (aIRR: $_{0.29}0.40_{0.56}$). We have also shown that the population-level changes in DDKT rates have had a direct impact on the individual-level cumulative incidence of DDKT, such that the cumulative incidences of DDKT for cPRA groups have become more similar 3-years post-KAS. Despite these changes, we have also shown that waitlist mortality has not substantially changed for the HS post-KAS, with cPRA 98%+ candidates continuing to have an increased likelihood of waitlist mortality compared to non-HS candidates. Finally, while 1-year post-transplant mortality is unchanged for HS candidates post-KAS, cPRA 90-97%, 98%, and 99% candidates have a significantly lower risk of 1-year death-censored graft failure.

Our results are consistent with several studies published shortly after KAS implementation that described a significant short-term increase in DDKT rate for cPRA ≥ 98% candidates.[10-12, 29] However, we have extended this work by showing that KAS also affected DDKT rates of other HS candidates. Notably, we showed that cPRA 80-89% candidates have a lower DDKT rate 3 years post-KAS compared to pre-KAS. We also showed that despite this decline, they were not disadvantaged by this change, but rather their DDKT rate became more similar to other cPRA groups. Additionally, we have demonstrated that KAS led to more balanced access to DDKT for the HS. For example, cPRA 99.9%+ candidates had a 3-year cumulative incidence of DDKT of 20.2%

post-KAS compared to 30.7% for non-HS candidates, whereas pre-KAS they had a cumulative incidence of 4.2% and 32.1%, respectively. Importantly, the proportion of DDKT recipients with a prior kidney transplant increased only slightly (14.7% post-KAS vs. 13.0% pre-KAS), suggesting that the large changes in access to DDKT for the HS were not driven primarily by prioritization of candidates with a prior kidney transplant. Although HS candidates are now transplanted out of proportion to their prevalence on the waitlist, the dramatic improvement in DDKT rates has led to an allocation system where they now have a realistic likelihood undergoing DDKT, without significantly affecting likelihood of DDKT for non-HS candidates.

This relative homogenization of DDKT rates based on cPRA is a remarkable accomplishment given the profound disparities that existed prior to KAS, and is consistent with the European experience with the Eurotransplant Acceptable Mismatch program.[20, 21, 30-32] Although implemented over 25 years ago, this program was developed in response to a growing concentration of HS candidates (defined in this program as cPRA ≥ 85%) on the waitlist in a number of European countries.[30] This program defines acceptable antigens for transplantation in the HS candidate, and then mandates sharing of organs across participating countries to any patient with a cPRA ≥ 85% who has no mismatches with the donor organ.[30] After implementation, access to DDKT improved for HS candidates, as the number of organ offers they received increased and their waiting times to DDKT decreased.[32] Thus, the success of KAS has mirrored the success of other transplant programs designed to facilitate DDKT among HS candidates.

Although KAS has led to more balanced access to DDKT across cPRA groups, there continue to be important differences in DDKT rates. Notably, cPRA 99.5-99.9% candidates have a substantially higher likelihood of DDKT compared to non-HS candidates (aSHR: $_{1.74}2.08_{2.47}$, $p<0.001$), whereas cPRA 99.9% + candidates have a lower likelihood (aSHR: $_{0.49}0.60_{0.75}$, $p<0.001$). This is consistent with a study showing that cPRA 100% candidates represent a group of candidates who can have

varying access to DDKT based on their unrounded cPRA.[6] Since KAS awards the same amount of allocation points to all cPRA 100% candidates, regardless of their unrounded cPRA, it is not unexpected that cPRA 99.5-99.9% candidates would be significantly more likely to find a match than cPRA 99.9%+ candidates. If future policy changes to KAS were to be considered, the exact amount of bonus points awarded to cPRA 100% candidates should consider the differing likelihood of DDKT based on their unrounded cPRA value.

Finally, the overall increase in DDKT rates for HS candidates that we report here may shed some light on an important issue – how to best manage the highly sensitized patient. Highly sensitized patients represent a challenging group of patients to manage as they face significant risks both before and after transplantation including increased waitlist mortality, higher rates of delayed graft function, acute rejection, and graft loss.[6, 20, 21, 33-38] As a result of these, a number of alternative transplantation techniques have been developed – including kidney-paired donation (KPD) and incompatible living donor kidney transplantation (ILDKT).[23, 24, 39-43] We have previously shown that ILDKT confers a survival benefit compared to entering the deceased donor waiting list and then potentially undergoing DDKT.[24] However, this study was conducted before KAS. As DDKT rates have significantly changed for HS candidates after KAS, it is possible that the survival benefit of ILDKT after KAS may be different. Moreover, the use of KPD has expanded, and dramatic variation exists in time to KPD depending on a particular patient's cPRA and blood type.[44] In light of the vast improvement in access to DDKT that we report here, the relative benefit of each transplantation method compared to the others should be revisited.

Our study has some limitations that merit further discussion. First, in using national registry data the presence of missing data and data entry error is unavoidable. However, the data that we used is typically of high quality since it is critical to organ allocation priority.[25] In our study, missing data were minimal and thus unlikely to change inferences – for example, cPRA was missing for <0.01%

of candidates. Secondly, in comparing relative DDKT rates we adjusted for variables known to be associated with access to DDKT. However, we are unable to control for unmeasured confounders that also affect this rate (such as cardiovascular comorbidities that may be more prevalent in HS candidates and are associated with waitlist mortality, precluding DDKT). Although unlikely, it is possible that these confounders could alter the relationship between cPRA, KAS, and DDKT rates that we have described. Additionally, our study was not designed to quantify whether the effect of KAS was different for HS candidates in different geographic regions. However, the HS candidates that benefited from KAS (cPRA > 98%) receive local, regional, and national sharing priority, such that geographic differences in how KAS affected these candidates should be relatively small. Nevertheless, we acknowledge that geography continues to remain an important determinant of access to DDKT under KAS.[45]

In conclusion, we have shown that KAS has been successful at increasing DDKT rates for the most HS candidates (cPRA > 98%). Although substantial imbalance in DDKT rates continue to exist for cPRA 99.5-99.9% and 99.9%+ candidates, relative DDKT rates between cPRA categories have become more homogenous. Although KAS has not resulted in a perfectly equitable system, it has led to more balanced DDKT rates for candidates of all cPRA groups.

Table 1. Baseline Characteristics of Deceased Donor Kidney Transplant Recipients Pre-KAS† and Post-KAS

Characteristics	Pre-KAS (N = 30,031)	Post-KAS (N = 35,172)	*P*
Age in years, mean (SD^)	53.9 (12.8)	52.4 (13.1)	<0.001
Female, N (%)	11,793 (39.3)	14,212 (40.4)	0.003
Race, N (%)			<0.001
White	12,801 (42.6)	12,740 (36.2)	
Black	9,672 (32.2)	12,503 (35.5)	
Hispanic	4,853 (16.2)	6,580 (18.7)	
Other	2,705 (9.0)	3,349 (9.5)	
ABO Blood Type, N (%)			0.07
O	13,581 (45.2)	16,082 (45.7)	
A	7,177 (36.6)	11,316 (35.5)	
B	2,512 (12.8)	4,284 (13.4)	
AB	994 (5.1)	1,733 (5.4)	
Calculated panel-reactive antibody, N (%)			<0.001
0-79%	25,161 (83.8)	27,824 (79.1)	
80-89%	2,041 (6.8)	1,162 (3.3)	
90-97%	1,837 (6.1)	1,805 (5.1)	
98%	291 (1.0)	420 (1.2)	
99%	405 (1.4)	1,054 (3.0)	
100%	296 (1.0)	2,907 (8.3)	
Sharing of donor organ, N (%)			<0.001
Local	23,310 (77.6)	24,205 (68.8)	
Regional	2,711 (9.0)	4,679 (13.3)	
National	4,010 (13.4)	6,288 (17.9)	
Time spent on dialysis in years, median (IQR#)	2.3 (0.8-4.0)	4.6 (2.7-6.9)	<0.001
History of prior kidney transplant, N (%)	3,893 (13.0)	5,184 (14.7)	<0.001
Estimated Post-Transplant Survival score, mean (SD^)	46.4 (28.5)	45.8 (29.6)	0.002

†kidney allocation system ^standard deviation #interquartile range

Table 2. Relative Rates of Deceased Donor Kidney Transplantation For Various cPRA* Categories by Months Post-KAS†

cPRA	0-6 mos	6-12 mos	12-18 mos	18-24 mos	24-30 mos	30-36 mos	*P*
80-89%	$_{0.19}$**0.24**$_{0.30}$	$_{0.21}$**0.27**$_{0.35}$	$_{0.23}$**0.31**$_{0.41}$	$_{0.30}$**0.39**$_{0.49}$	$_{0.30}$**0.40**$_{0.53}$	$_{0.35}$**0.45**$_{0.58}$	<0.001
90-97%	$_{0.53}$**0.65**$_{0.81}$	$_{0.65}$**0.78**$_{0.93}$	$_{0.75}$0.91$_{1.10}$	$_{0.89}$1.09$_{1.35}$	$_{0.91}$1.16$_{1.49}$	$_{0.97}$1.26$_{1.64}$	<0.001
98%	$_{1.09}$**1.40**$_{1.81}$	$_{0.86}$1.32$_{2.01}$	$_{1.41}$**1.94**$_{2.67}$	$_{1.37}$**2.00**$_{2.92}$	$_{1.42}$**2.02**$_{2.86}$	$_{1.27}$**1.77**$_{2.46}$	0.2
99%	$_{2.68}$**3.42**$_{4.37}$	$_{2.91}$**3.66**$_{4.59}$	$_{2.60}$**3.70**$_{5.26}$	$_{2.98}$**4.28**$_{6.14}$	$_{3.33}$**4.52**$_{6.14}$	$_{3.18}$**4.36**$_{5.98}$	0.6
99.5-99.9%	$_{15.06}$**19.58**$_{25.47}$	$_{16.40}$**21.09**$_{27.13}$	$_{14.02}$**19.49**$_{27.09}$	$_{17.63}$**23.37**$_{30.99}$	$_{17.93}$**24.15**$_{32.53}$	$_{16.91}$**24.29**$_{34.89}$	0.4
99.9%+	$_{6.71}$**8.39**$_{10.48}$	$_{7.94}$**10.35**$_{13.49}$	$_{6.87}$**8.60**$_{10.77}$	$_{8.15}$**10.40**$_{13.28}$	$_{6.45}$**8.71**$_{11.75}$	$_{8.79}$**11.58**$_{15.26}$	0.1

Relative rates are presented as the relative rate of transplantation for a given cPRA category in the months following implementation of KAS compared to the pre-KAS era. *P*-values are testing for trends within each cPRA category; significant values suggest transplant rates are changing over time. Bolded values represent relative DDKT rates in that time period that are significantly different than 1.0 ($p<0.05$)

*calculated panel reactive antibody †kidney allocation system

Table 3. Rates of Deceased Donor Kidney Transplantation For Various cPRA* Categories Comparing HS+ Candidates to non-HS+ Candidates

cPRA	Pre-KAS	Months Post-KAS 0-6 mos	6-12 mos	12-18 mos	18-24 mos	24-30 mos	30-36 mos	*P*
80-89%	**2.69 3.27 3.97**	0.97 1.26 1.64	**1.03 1.26 1.55**	**1.11 1.38 1.71**	**1.32 1.64 2.04**	**1.35 1.66 2.04**	**1.50 1.79 2.14**	<0.001
90-97%	**1.01 1.19 1.40**	0.91 1.26 1.75	**1.04 1.33 1.70**	**1.11 1.48 1.96**	**1.24 1.68 2.29**	**1.27 1.75 2.29**	**1.43 1.82 2.32**	0.006
98%	**0.35 0.44 0.55**	0.67 1.00 1.45	0.52 0.83 1.31	0.76 1.16 1.77	0.73 1.14 1.76	0.75 1.12 1.68	0.65 0.94 1.36	0.33
99%	**0.24 0.29 0.35**	**1.16 1.62 2.27**	**1.12 1.53 2.10**	0.98 1.48 2.23	**1.19 1.78 2.65**	**1.28 1.78 2.48**	**1.19 1.68 2.38**	0.97
99.5-99.9%	**0.10 0.12 0.15**	**2.75 3.79 5.22**	**2.67 3.60 4.87**	**2.19 3.18 4.61**	**2.54 3.61 5.12**	**2.57 3.64 5.15**	**2.46 3.50 4.98**	0.85
99.9%+	**0.02 0.03 0.04**	**0.29 0.39 0.53**	**0.32 0.43 0.57**	**0.27 0.34 0.43**	**0.29 0.39 0.53**	**0.22 0.32 0.46**	**0.29 0.40 0.56**	0.15

Relative rates are presented as the relative rate of transplantation for a given cPRA category compared to cPRA 0-79%. *P*-values are testing for trends post-KAS within each cPRA category; significant values suggest transplant rates after KAS are changing over time. Bolded values represent a relative DDKT rate within that time period that is significantly different than 1 ($p<0.05$)

*calculated panel reactive antibody †kidney allocation system +highly sensitized

Table 4. Cumulative Incidence of Deceased Donor Kidney Transplantation Pre-KAS† and Post-KAS†

	Pre-KAS† (%)			Post-KAS† (%)		
cPRA*	**1-year**	**2-year**	**3-year**	**1-year**	**2-year**	**3-year**
0-79%	$_{12.3}12.5_{12.7}$	$_{22.0}22.2_{22.5}$	$_{31.8}32.1_{32.5}$	$_{13.8}14.0_{14.2}$	$_{22.1}22.3_{22.6}$	$_{30.4}30.7_{31.1}$
80-89%	$_{26.3}28.1_{30.0}$	$_{37.4}39.6_{41.7}$	$_{42.1}44.4_{46.7}$	$_{17.7}19.3_{20.9}$	$_{28.5}30.4_{32.4}$	$_{35.9}38.1_{40.4}$
90-97%	$_{17.6}18.8_{20.1}$	$_{27.5}29.0_{30.6}$	$_{33.9}35.7_{37.4}$	$_{20.4}21.7_{23.0}$	$_{32.2}33.8_{35.4}$	$_{39.6}41.4_{43.2}$
98%	$_{9.1}10.8_{12.7}$	$_{17.5}19.9_{22.4}$	$_{22.9}25.7_{28.6}$	$_{17.2}19.4_{21.8}$	$_{29.4}32.2_{35.0}$	$_{36.0}39.1_{42.2}$
99%	$_{6.4}7.5_{8.7}$	$_{13.6}15.2_{16.9}$	$_{18.4}20.3_{22.3}$	$_{24.3}26.2_{28.1}$	$_{35.8}38.0_{40.2}$	$_{42.4}44.8_{47.2}$
99.5-99.9%	$_{3.2}3.9_{4.8}$	$_{6.9}8.0_{9.2}$	$_{10.6}12.1_{13.6}$	$_{31.0}32.9_{34.8}$	$_{40.9}43.0_{45.1}$	$_{46.2}48.4_{50.5}$
99.9%+	$_{1.0}1.4_{1.9}$	$_{2.4}3.0_{3.8}$	$_{3.5}4.2_{5.1}$	$_{8.5}9.4_{10.4}$	$_{14.6}15.9_{17.1}$	$_{18.7}20.2_{21.6}$

Cumulative incidence and 95% confidence interval of DDKT calculated using a competing risk framework, accounting for waitlist mortality or removal from waitlist due to deteriorating medical status.

*calculated panel reactive antibody †kidney allocation system

Table 5. Cumulative Incidence of Waitlist Mortality Pre-KAS† and Post-KAS†

	Pre-KAS† (%)			Post-KAS† (%)		
cPRA*	**1-year**	**2-year**	**3-year**	**1-year**	**2-year**	**3-year**
0-79%	$_{4.4}4.6_{4.7}$	$_{9.8}10.0_{10.2}$	$_{15.7}16.0_{16.3}$	$_{4.8}5.0_{5.1}$	$_{11.1}11.3_{11.5}$	$_{17.5}17.8_{18.0}$
80-89%	$_{3.4}4.2_{5.0}$	$_{7.3}8.5_{9.8}$	$_{11.3}12.8_{14.5}$	$_{3.9}4.7_{5.6}$	$_{10.2}11.6_{13.0}$	$_{14.7}16.4_{18.2}$
90-97%	$_{3.9}4.6_{5.3}$	$_{8.9}9.9_{11.0}$	$_{14.4}15.8_{17.2}$	$_{4.3}5.0_{5.7}$	$_{10.3}11.3_{12.5}$	$_{15.4}16.7_{18.2}$
98%	$_{2.7}3.7_{5.0}$	$_{8.1}9.8_{11.8}$	$_{12.9}15.2_{17.7}$	$_{4.8}6.0_{7.5}$	$_{11.3}13.2_{15.4}$	$_{16.0}18.5_{21.1}$
99%	$_{4.7}5.6_{6.6}$	$_{9.6}11.0_{12.5}$	$_{16.0}17.9_{19.8}$	$_{4.9}5.8_{6.9}$	$_{10.1}11.6_{13.1}$	$_{14.1}15.9_{17.7}$
99.5-99.9%	$_{5.2}6.1_{7.2}$	$_{12.0}13.4_{15.0}$	$_{19.4}21.3_{23.2}$	$_{5.2}6.1_{7.2}$	$_{10.8}12.2_{13.6}$	$_{15.0}16.6_{18.4}$
99.9%+	$_{4.2}5.0_{5.9}$	$_{10.7}11.9_{13.2}$	$_{18.3}19.9_{21.6}$	$_{6.6}7.4_{8.3}$	$_{13.3}14.5_{15.8}$	$_{20.2}21.8_{23.3}$

Cumulative incidence and 95% confidence interval of waitlist mortality calculated using a competing risk framework, accounting for deceased donor kidney transplantation.

*calculated panel reactive antibody †kidney allocation system

Table 6. Relative Likelihood of Deceased Donor Kidney Transplantation and Waitlist Mortality for Highly Sensitized Candidates Compared to Non-Highly Sensitized Candidates post-KAS.

	aSHR	
cPRA*	DDKT#	Waitlist Mortality
0-79%	Ref	Ref
80-89%	**1.19 1.34 1.51**	0.86 1.02 1.22
90-97%	**1.24 1.48 1.77**	0.97 1.14 1.35
98%	**1.14 1.37 1.64**	**1.16 1.44 1.80**
99%	**1.42 1.73 2.10**	**1.06 1.27 1.52**
99.5-99.9%	**1.74 2.08 2.47**	**1.19 1.44 1.74**
99.9%+	**0.49 0.60 0.75**	**1.59 1.89 2.25**

Adjusted subhazard ratios (aSHR) represent the relative likelihood for a given cPRA category to experience the outcome of interest compared to cPRA 0-79% candidates, accounting for competing risks. For example cPRA 99.9%+ candidates are 60% as likely as otherwise similar cPRA 0-79% candidates to undergo DDKT post-KAS, account for their competing risk of waitlist mortality. Bolded values represent a ratio that significantly different than 1.0 ($p<0.05$).

#Deceased donor kidney transplantation, *calculated panel reactive antibody

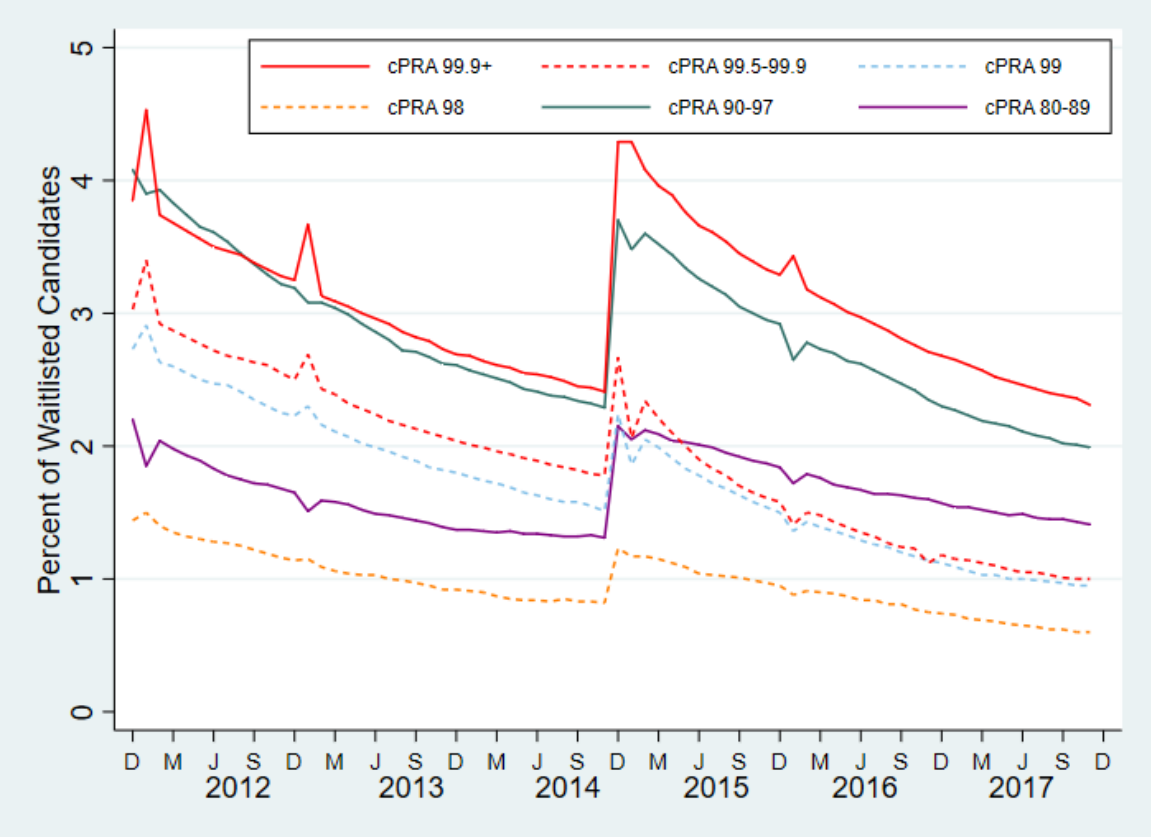
Table 7. One Year Post-Transplant Mortality and Death-Censored Graft Failure for Highly Sensitized Candidates Post-KAS Compared to Pre-KAS.

	aHR	
cPRA*	Mortality	Graft Failure
80-89%	$_{0.48}0.77_{1.25}$	$_{0.38}0.64_{1.06}$
90-97%	$_{0.54}0.79_{1.13}$	$\mathbf{_{0.29}0.43_{0.62}}$
98%	$_{0.43}1.13_{2.95}$	$\mathbf{_{0.11}0.26_{0.63}}$
99%	$_{0.47}0.87_{1.64}$	$\mathbf{_{0.17}0.36_{0.77}}$
99.5-99.9%	$_{0.47}1.00_{2.10}$	$_{0.33}0.72_{1.60}$
99.9%+	$_{0.29}0.72_{1.76}$	$_{0.31}0.66_{1.43}$

Adjusted hazard ratios (aHR) represent the relative risk of 1-year post-transplant mortality or death-censored graft failure for HS candidates post-KAS. For example cPRA 99.9%+ candidates are at a similar risk of 1-year post-transplant mortality post-KAS compared to pre-KAS. Bolded values represent a ratio that significantly different than 1.0 ($p<0.05$).

#Deceased donor kidney transplantation, *calculated panel reactive antibody

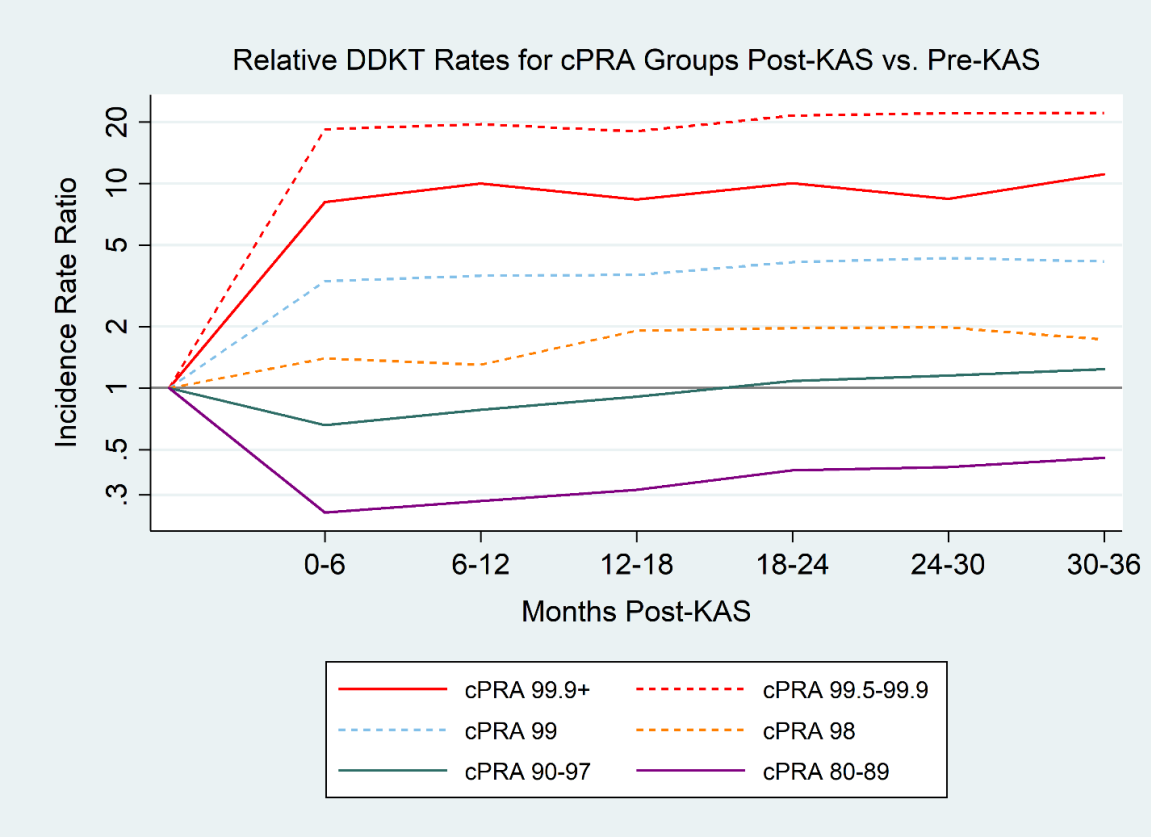
Figure 1. Monthly prevalence of highly sensitized candidates on the waitlist during the study period.



Post-KAS, cPRA 99.9%+ candidates represent the most common group of highly sensitized candidates on the waitlist. After an initial increase in the prevalence of highly sensitized candidates immediately after KAS, these candidates now represent a smaller proportion of the waitlist.

cPRA, calculated panel reactive antibody; D, December; M, March; J, June; S, September

Figure 2. Relative DDKT# Rates for Different cPRA* Groups Post-KAS Compared to Pre-KAS

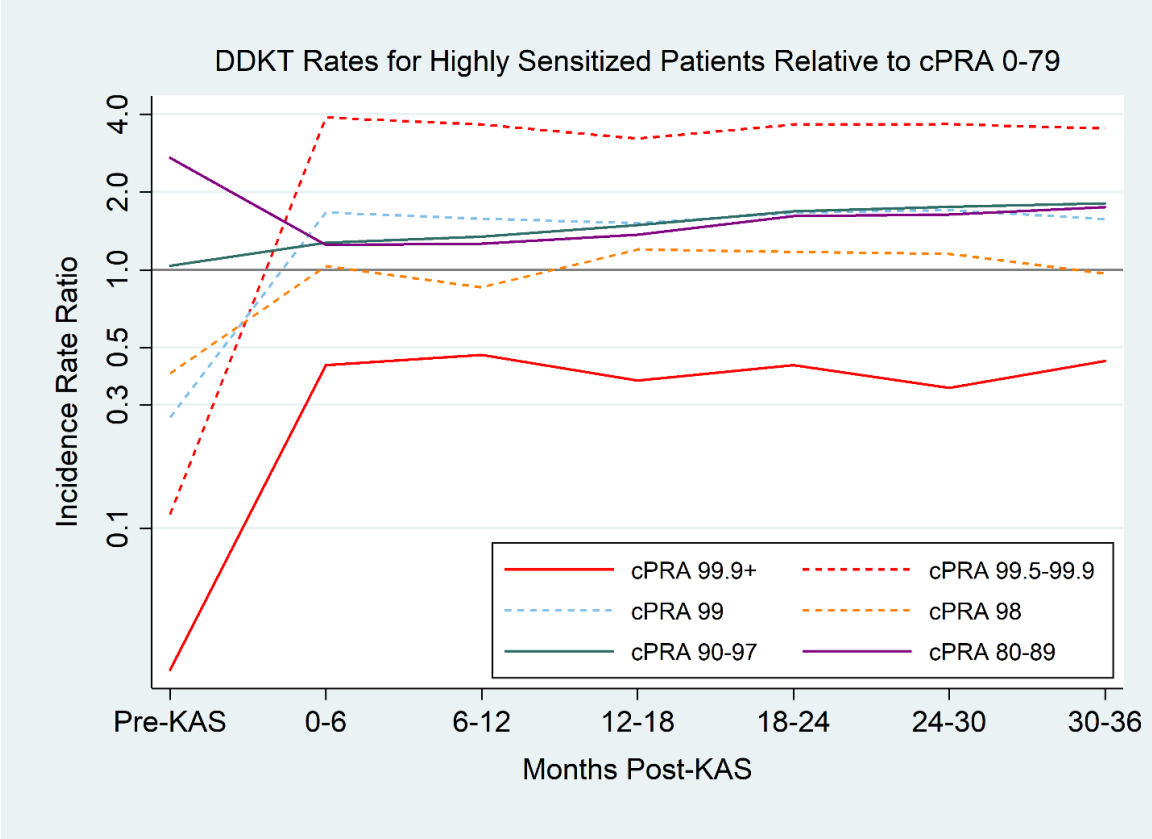


KAS has produced sustained changes to DDKT rates for most cPRA categories. Three years post-KAS, cPRA 99.9%+, 99.5-99.9%, 99%, and 98% candidates have increased DDKT rates compared to pre-KAS. Conversely, cPRA 80-89% candidates have lower DDKT rates post-KAS compared to pre-KAS.

#DDKT, deceased donor kidney transplantation; *cPRA, calculated panel reactive antibody

Grey horizontal line represents an incidence rate ratio of 1, which would represent equivalent DDKT rates post-KAS compared to pre-KAS

Figure 3. Relative DDKT# Rates for Different cPRA* Groups Compared to cPRA 0-79

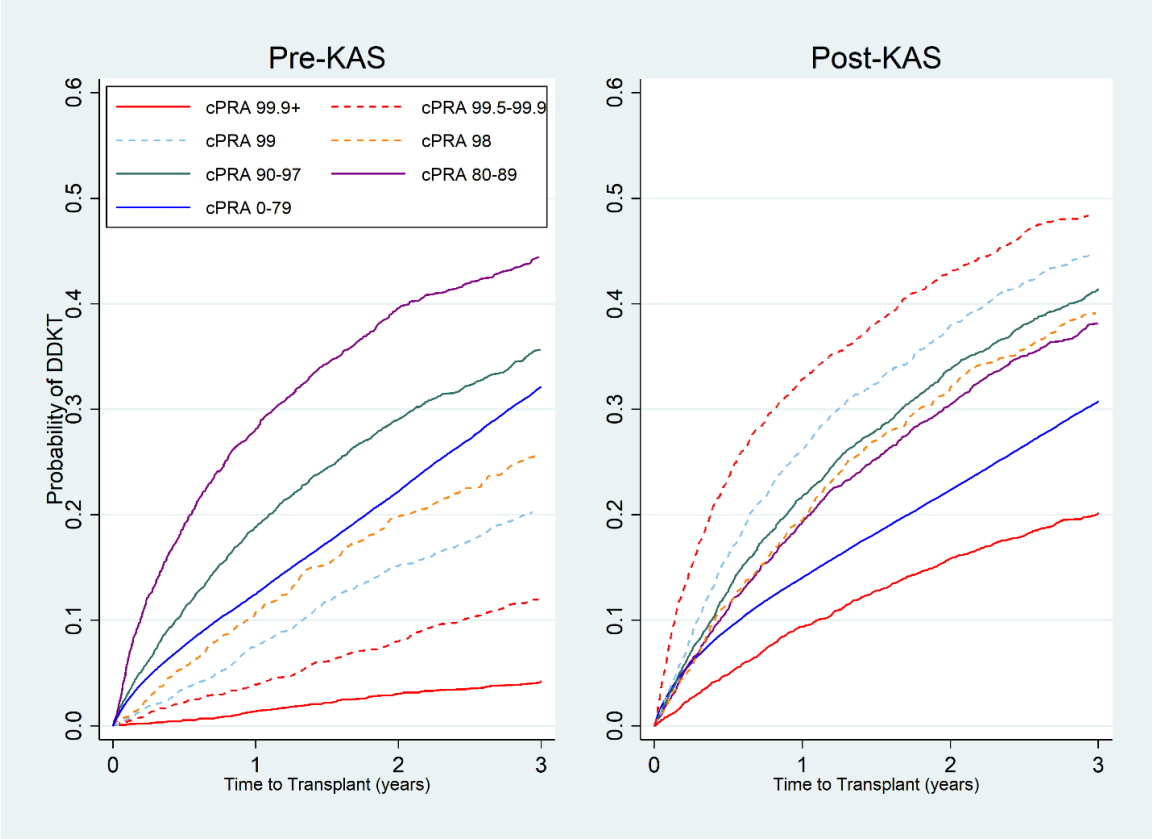


DDKT rates become more balanced across cPRA groups post-KAS. However, cPRA 99.5-99.9% are transplanted at a substantially higher rate than 0-79% candidates post-KAS, whereas cPRA 99.9%+ candidates are transplanted at a lower rate.

#DDKT, deceased donor kidney transplantation; *cPRA, calculated panel reactive antibody

Grey horizontal line represents an incidence rate ratio of 1, which would represent equivalent DDKT rates between a given cPRA category and cPRA 0-79%.

Figure 4. Cumulative incidence of DDKT# for different cPRA* groups pre-KAS and post-KAS.

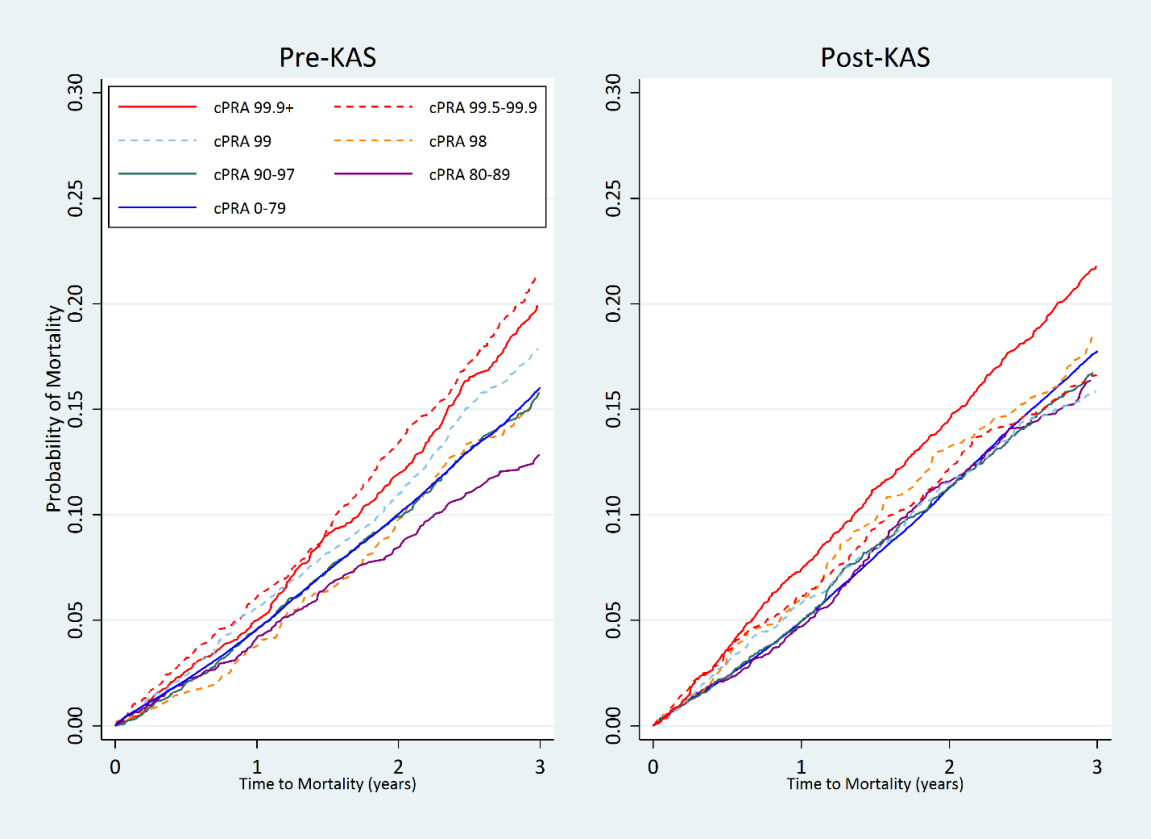


The cumulative incidence of DDKT becomes more similar between cPRA groups following KAS compared to before KAS. Pre-KAS and Post-KAS, cPRA 99.9%+ candidates have the lowest cumulative incidence of DDKT

#DDKT, deceased donor kidney transplantation; *cPRA, calculated panel reactive antibody

Cumulative incidence of DDKT estimated under a competing risks framework, accounting for a candidate's competing risk of death or removal from the waitlist due to deteriorating medical condition

Figure 5. Cumulative incidence of waitlist mortality for different cPRA* groups pre-KAS and post-KAS.



The cumulative incidence of waitlist remains similar between cPRA groups post-KAS and pre-KAS.

*cPRA, calculated panel reactive antibody

Cumulative incidence of waitlist mortality estimated under a competing risks framework, accounting for a candidate's competing risk of deceased donor kidney transplantation

Chapter 3. How Do Highly Sensitized Patients Get Kidney Transplants in the United States? Trends Over The Last Decade

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ABSTRACT

Prioritization of highly sensitized (HS) candidates under the Kidney Allocation System (KAS) and growth of large, multi-center kidney-paired donation (KPD) clearinghouses have broadened the transplant modalities available to HS candidates. To quantify temporal trends in utilization of these modalities, we used SRTR data from 2009-2017 to study 39,907 adult HS (cPRA≥80%) waitlisted candidates and 19,003 recipients. We used competing risks regression to quantify temporal trends in likelihood of DDKT, KPD, and non-KPD LDKT for HS candidates (Era 1: 01/01/2009-12/31/2011; Era 2: 01/01/2012-12/3/2014; Era 3: 12/4/2014-12/31/2017). Although the likelihood of DDKT and KPD increased over time for all HS candidates (adjusted subhazard ratio [aSHR] Era 3 vs. 1 for DDKT: $_{1.74}1.85_{1.97}$, p<0.001 and for KPD: $_{1.70}2.20_{2.84}$, p<0.001), the likelihood of non-KPD LDKT decreased (aSHR: $_{0.69}0.82_{0.97}$, p=0.02). However, these changes impacted HS recipients differently based on cPRA. Among recipients, more cPRA 98-99.9% and 99.9%+ recipients underwent DDKT (96.2% in Era 3 vs. 59.1% in Era 1 for cPRA 99.9%+), whereas fewer underwent non-KPD LDKT (1.9% vs. 30.9%) or KPD (2.0% vs. 10.0%). Although KAS increased DDKT likelihood for the most HS candidates, it also decreased the use of non-KPD LDKT to transplant cPRA 98%+ candidates.

INTRODUCTION

Highly sensitized (HS) kidney transplant candidates have historically faced substantial difficulty achieving transplantation, with a much lower likelihood of deceased donor kidney transplantation (DDKT) and kidney-paired donation (KPD) compared to non-HS candidates.[6, 20, 22, 46, 47] However, recent changes to the deceased donor allocation system, and the growth of large single- and multi-center kidney-paired donation (KPD) clearinghouses, have broadened the different transplant modalities available to HS candidates.[48, 49] The Kidney Allocation System (KAS), introduced in 2014, instituted a sliding scale system that gives increasing priority for DDKT candidates with higher levels of sensitization.[1, 4] Under KAS, candidates with a calculated panel reactive antibody (cPRA) ≥98% have seen an increase in DDKT rates (from a 1.77-fold increase for cPRA 98% candidates to an 11.58-fold increase for cPRA 99.9%+ candidates).[50] Concomitantly, KPD use has increased over time. In a study of the largest KPD clearinghouse in the United States, the number of KPD transplants performed annually increased from 21 in 2006 to 399 in 2016.[49]

However, these studies focused on a single modality (either DDKT or KPD), and do not address the clinical reality that the modality chosen for a HS candidate depends on the relative likelihood of all available transplant options - DDKT, KPD, or non-KPD living donor kidney transplantation (LDKT). No studies have compared the joint effect of changes in the likelihood of all transplant modalities now available to the HS. Additionally, it is possible that the relative likelihood of each transplant modality varies across cPRA, and that the net impact of these different likelihoods resulted in different patterns of modality usage across cPRA.[44, 50] For example, the substantial increase in DDKT rates for cPRA ≥98% candidates under KAS might have led to disproportionately more DDKT use, despite an overall increase in the use of KPD in this group. Conversely, decreased DDKT priority for cPRA 80-89% candidates might have led to a substantial increase in KPD or non-KPD LDKT use in this group.[50] Characterization of how these changes have acted together

would allow for a better assessment of how DDKT policy change and clinical expansion of KPD have improved the ability of HS candidates to undergo transplant in the broader context of all available transplant modalities.

To better understand changes in how HS patients have been treated and transplanted over the last decade, we used national registry data to study utilization of different transplant modalities over time, and how this varied across cPRA. The goals of our study were (i) to quantify temporal trends in likelihood of DDKT, KPD, and non-KPD LDKT for HS candidates, and (ii) to understand how these changes affected the modalities ultimately used by HS recipients.

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, waitlisted candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[25] The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study population

We included all adult (age ≥18 years) HS (cPRA ≥80%) kidney-only waitlist candidates and transplant recipients between 1/1/2009 and 12/31/2017. The unit of analysis was the candidate, and only the first high-cPRA registration per candidate was included. This study was approved by the Johns Hopkins University Institutional Review Board.

Time periods

We categorized candidates by date of listing, and recipients by date of transplant, into 3 eras (Era 1: 1/1/2009 – 12/31/2011, Era 2: 1/1/2012 – 12/3/2014, and Era 3: 12/4/2014-12/31/2017). We divided Era 2 and 3 on 12/4/2014 to reflect KAS implementation. These time periods were selected to best represent hypothesized changes over time in the use of both DDKT and KPD, and not just one single modality. In order to understand how changes in transplant modality usage changed over time, we chose the earliest era (Era 1) as our reference era. As a sensitivity analysis, we divided Era 3 into two separate 18-month periods to determine whether a 'bolus effect' was influencing trends in this era. Results of this were consistent with our main analysis.

cPRA ascertainment and categorization

cPRA values for candidates and recipients were obtained from the SRTR cPRA history dataset, which contains time-varying measurements of cPRA for every DDKT waitlist candidate. Some recipients underwent KPD or non-KPD LDKT directly and were never placed on the waitlist for DDKT, and thus did not have a cPRA recorded in the cPRA history dataset. For these recipients, we obtained their cPRA from the candidate peak cPRA composite variable, which contains the peak cPRA recorded from one of several additional cPRA variables (e.g. from the recipient histocompatibility form). We excluded recipients who did not have any cPRA recorded in any variable (n=366, 0.09%).

We divided our study population into the following cPRA categories: 80-89%, 90-97%, 98-99.9%, and 99.9%+. These categories were selected to best balance anticipated differences in likelihood of both DDKT and KPD across cPRA based on our prior work, while still maintaining sufficient groups sizes for well-powered comparisons.[44, 50] As a sensitivity analyses, we also explored the following alternative cPRA categorization: 80-89%, 90-97%, 97.5-98.49%, 98.5-99.49%, and 99.5%+.

Temporal trends in transplant likelihood for HS candidates

In order to understand how the likelihood of each transplant modality (DDKT, KPD, and non-KPD LDKT) changed over time for transplant candidates, we used competing risks regression with the method of Fine and Gray.[27] The use of KPD was distinguished from non-KPD LDKT using the living donor relationship field as reported to the OPTN, and we considered KPD transplants to be those coded as 'non-biological, unrelated: paired donation' or 'non-biological, unrelated: non-directed donation'. For each modality, and across cPRA groups, we constructed a separate model treating death or waitlist removal due to deteriorating medical condition, the remaining two modalities, and waitlist removal for any other reason as competing events (e.g. if DDKT was the outcome, then KPD, non-KPD LDKT, death/waitlist removal due to deteriorating medical condition, and waitlist removal were all treated as competing events). Candidates entered the risk set on the day of listing if the candidate had a cPRA ≥80%, whereas candidates who entered the waitlist but had an initial cPRA <80% were treated as late entries when their cPRA reached ≥80%. Candidates in the risk set whose cPRA dropped below 80% were censored, but their waitlist time up until that point was included in the analysis. Candidates remaining on the waitlist at era changes were censored, and were otherwise followed until three years, or until administrative censorship on 2/28/2019. Analyses stratified by cPRA were only adjusted for candidate age, sex, and race due to a small number of events in certain subgroups.

Temporal trends in transplant modality used for HS recipients

To understand how the differing likelihood of each transplant modality for HS transplant candidates impacted which transplant modalities were used by recipients, we compared the proportion of HS recipients who received each modality (DDKT, KPD, non-KPD) across cPRA groups and time eras using the chi-square test.

Use of non-KPD LDKT for HS recipients

In our initial analysis, we found that a significantly lower proportion of cPRA 98%+ recipients used non-KPD LDKT in Era 3 compared to Era 1. In order to understand whether this was due to a direct decrease in the transplant type (e.g. non-KPD LDKT vs. any other) used for HS recipients, we used logistic regression to predict the number of HS candidates expected to undergo non-KPD LDKT in each era. Our outcome was a binary variable for whether or not the candidate underwent non-KPD LDKT. We controlled for candidate age, sex, race, blood type, cause of ESRD, previous transplant, time on dialysis, and waitlist time to reach cPRA ≥80%. The prediction model for receiving non-KPD LDKT was derived using candidates from Era 1. To obtain the cumulative number of expected events in each era, and for each cPRA group, we summed the individual predicted probabilities of non-KPD LDKT for each recipient in that era. We then divided the observed number of patients who actually received non-KPD LDKT by the cumulative number of expected events to yield an observed versus expected (O:E) ratio for each era/cPRA group. We calculated the 95% confidence intervals for the O:E ratio using the method outlined in the SRTR Technical Methods for the Program Specific Report (https://www.srtr.org/about-the-data/technical-methods-for-the-program-specific-reports). Effectively, this model allowed us to distinguish between a direct decrease in the usage of non-KPD LDKT over time (O:E ratio <1), or an increase in the number of candidates undergoing DDKT (or KPD) who might not have otherwise been transplanted (O:E ratio ≥1).

Statistical analysis

Confidence intervals are reported as per the method of Louis and Zeger.[28] All analyses were performed using Stata 16.0/IC for Windows (College Station, Texas).

RESULTS

Study population

HS candidates

We identified 39,907 HS candidates, of which 14,595 (36.6%) were listed in Era 1, 13,487 (33.8%) were listed in Era 2, and 11,825 (29.6%) were listed in Era 3. Compared to candidates in Era 1, candidates in Era 3 were older (49.7 years vs. 48.4 years, p<0.001), less likely to be white (37.5% vs. 41.2%, p<0.001), more likely to have ESRD caused by glomerular disease (27.8% vs. 28.4%, p<0.001), more likely to have a higher median cPRA (94.0% vs. 92.0%, p<0.001), and had a higher estimated post-transplant survival score (49.7 vs. 49.5, p<0.001). Candidates in Era 3 spent less time on dialysis (1.8 years vs. 2.5 years, p<0.001) and were less likely to have had a prior transplant (44.0% vs. 48.3%, p<0.001) (Table 1).

HS recipients

We identified 19,003 HS recipients, of which 5,098 (26.8%) were transplanted in Era 1, 5,531 (29.1%) were transplanted in Era 2, and 8,374 (44.1%) were transplanted in Era 3. Compared to recipients in Era 1, recipients in Era 3 were more likely to be older (49.3 years vs. 48.6 years, p=0.02), less likely to be white (41.3% vs. 48.5%, p<0.001), more likely to be blood type O (51.1% vs. 48.5%, p=0.002), more likely to be cPRA 100% (13.1% vs. 2.8%, p<0.001), more likely to have spent longer on dialysis (median 3.9 years vs. 3.5 years, p<0.001) and more likely to have had a prior transplant (52.6% vs. 46.9%, p<0.001) (Table 2).

Temporal trends in transplant likelihood for HS candidates

Overall temporal trends

Compared to candidates in Era 1, candidates in Era 3 were more likely to receive DDKT (adjusted subhazard ratio [aSHR]: $_{1.74}1.85_{1.97}$, p<0.001). Although there were no statistically significant changes in the likelihood of receiving any LDKT across eras (aSHR for Era 2 vs. 1: $_{0.86}1.00_{1.16}$, p=1.0; for Era 3 vs. 1: $_{0.99}1.13_{1.30}$, p=0.08) (Table 3), there were differences between types of LDKT. Candidates in Era 2 and 3 were more likely to receive KPD (aSHR for Era 2 vs. 1: $_{1.31}1.73_{2.29}$, p<0.001; for Era 3 vs.

1: $_{1.70}2.20_{2.84}$, p<0.001), but candidates in Era 2 and 3 were less likely to receive non-KPD LDKT compared to candidates in Era 1 (aSHR for Era 2 vs. 1: $_{0.65}0.78_{0.94}$, p=0.008; for Era 3 vs. 1: $_{0.69}0.82_{0.97}$, p=0.02). These changes led to a 3-year cumulative incidence of 38.6% for DDKT in Era 3 (vs. 25.4% in Era 1), 2.4% for KPD (vs. 1.2%), and 3.2% for non-KPD LDKT (vs. 3.9%) (Figure 1A-C).

Temporal trends by cPRA category

The trends highlighted above varied across cPRA. For candidates with cPRA 80-89%, candidates in Era 3 were less likely to receive DDKT (aSHR: $_{0.76}0.84_{0.92}$, p<0.001) compared to candidates in Era 1 (Table 3). Although there were no statistically significant changes in the likelihood of LDKT in Era 2, candidates were more likely to undergo KPD (aSHR: $_{1.02}1.53_{2.29}$, p=0.04), but less likely to undergo non-KPD LDKT (aSHR: $_{0.54}0.70_{0.92}$, p=0.01) compared to candidates in Era 1. However, candidates in Era 3 were more likely to undergo LDKT compared to Era 1 (aSHR: $_{1.05}1.27_{1.53}$, p=0.01), which was driven by an increase in the likelihood of KPD (aSHR: $_{1.41}2.03_{2.91}$, p<0.001). There were no statistically significant changes in the likelihood of non-KPD LDKT across eras. These changes led to a 3-year cumulative incidence of 36.3% for DDKT in Era 3 (vs. 40.7% in Era 1), 3.6% for KPD (vs. 1.7%), and 6.3% for non-KPD LDKT (vs. 6.1%) (Table 4, Figure 1D-F).

For candidates with cPRA 90-97%, candidates in Era 3 were more likely to receive DDKT (aSHR: $_{1.75}1.95_{2.17}$, p<0.001) compared to candidates in Era 1 (Table 3). Although there were no statistically significant changes in the likelihood of LDKT across eras, there was an increase in the likelihood of KPD (aSHR for Era 2 vs. 1: $_{1.25}1.98_{3.13}$, p=0.004; Era 3 vs. 1: $_{1.71}2.62_{4.00}$, p<0.001). There were no statistically significant changes in the likelihood of non-KPD LDKT across eras. These changes led to a 3-year cumulative incidence of 41.9% for DDKT in Era 3 (vs. 26.8% in Era 1), 3.1% for KPD (vs. 1.5%), and 2.8% for non-KPD LDKT (vs. 3.8%) (Table 4, Figure 1G-I).

For candidates with cPRA 98% to 99.9%, candidates in Era 3 were more likely to receive DDKT (aSHR: $_{5.57}6.62_{7.85}$, p<0.001) compared to candidates in Era 1 (Table 3). Although there were no statistically significant changes in the likelihood of LDKT, candidates in Era 3 were more likely to receive KPD (aSHR: $_{1.14}2.32_{4.73}$, p=0.02), but less likely to receive non-KPD LDKT than candidates in Era 1 (aSHR: $_{0.37}0.58_{0.92}$, p=0.02). These changes led to a 3-year cumulative incidence of 47.3% for DDKT in Era 3 (vs. 10.1% in Era 1), 1.4% for KPD (vs. 0.6%), and 1.5% for non-KPD LDKT (vs. 2.4%) (Table 4, Figure 1J-L).

For candidates with cPRA 99.9%+, candidates in Era 3 were more likely to receive DDKT (aSHR: $_{4.23}6.49_{9.96}$, p<0.001) compared to candidates in Era 1 (Table 3). However, there were no statistically significant changes in the likelihood of LDKT, non-KPD LDKT, or KPD across eras. These changes led to a 3-year cumulative incidence of 25.9% for DDKT in Era 3 (vs. 3.9% in Era 1), 0.5% for KPD (vs. 0.3%), and 0.6% for non-KPD LDKT (vs. 1.0%) (Table 4, Figure 1M-O).

Temporal trends in transplant modality used by HS recipients

Overall temporal trends

Over time, an increasing proportion of HS recipients were transplanted through DDKT (91.0% in Era 3 vs. 84.1% in Era 1, p<0.001) (Table 5, Figure 2). In contrast, a decreasing proportion of HS recipients were transplanted through non-KPD LDKT (4.8% vs. 11.6%). There were no significant changes in the proportion of recipients who underwent KPD (4.2% vs. 4.3%).

Temporal trends by cPRA category

The trends above varied across cPRA. A decreasing proportion of cPRA 80-89% recipients were transplanted through DDKT over time (80.1% in Era 3 vs. 86.2% in Era 1, p<0.001) (Table 5, Figure 2). In contrast, an increasing proportion were transplanted through KPD (8.6% vs. 3.8%). There were no substantial changes in the use of non-KPD LDKT (11.3% vs. 10.0%).

In contrast, an increasing proportion of cPRA 90-97% recipients were transplanted through DDKT (87.7% in Era 3 vs. 86.0% in Era 1, p<0.001) and KPD (5.9% vs. 4.2%), but fewer were transplanted through non-KPD LDKT (6.4% vs. 9.8%).

An increasing proportion of cPRA 98-99.9% and cPRA 99.9%+ recipients were transplanted through DDKT (95.8% in Era 3 vs. 78.7% in Era 1 for cPRA 98-99.9% recipients; 96.2% vs. 59.1% for cPRA 99.9%+ recipients, p<0.001) (Table 5, Figure 2). However, a decreasing proportion were transplanted through non-KPD LDKT (2.1% vs. 16.5% for cPRA 98-99.9% recipients; 1.9% vs. 30.9% for cPRA 99.9%+ recipients). Similarly, a decreasing proportion were transplanted through KPD (2.1% vs. 4.8% for cPRA 98-99.9% recipients; 2.0% vs. 10.0% for cPRA 99.9%+ recipients).

Likelihood of receiving non-KPD LDKT by era

Among cPRA 98-99.9% candidates, approximately one-third as many candidates underwent non-KPD LDKT in Era 3 as would have been expected given candidate characteristics (O:E: $_{0.46}0.67_{0.94}$) (Table 6). cPRA 99.9%+ candidates had an O:E ratio consistent with no change in non-KPD LDKT usage (O:E: $_{0.44}1.20_{2.61}$) although this comparison was limited by a small sample size (n=6 recipients in Era 3).

Sensitivity analyses

We also explored alternative cPRA categorizations to understand whether our findings were sensitive to these categories. Our results were consistent with our main analyses (Table 7). An increasing proportion of cPRA 97.5%-98.49% recipients underwent DDKT over time (88.0% in Era 3 vs. 78.2% in Era 1, p<0.001), as did cPRA 98.5%-99.49% recipients (93.8% vs. 80.3%, p<0.001) and cPRA 99.5%+ recipients (97.9% vs. 71.2%, p<0.001). However, a decreasing proportion of these

recipients underwent non-KPD LDKT (0.9% vs. 22.3% for 99.5%+ recipients) and KPD (1.2% vs. 6.5% for cPRA 99.5%+ recipients).

DISCUSSION

In this national study of 39,907 HS candidates and 19,003 recipients, we have shown that the likelihood of DDKT and KPD for HS candidates have increased by 1.85-fold and 2.20-fold, respectively, in Era 3 vs. Era 1. Conversely, HS candidates had an 18% decreased likelihood of non-KPD LDKT in Era 3 vs. Era 1. However, these changes varied across cPRA categories. The likelihood of KPD increased for cPRA 80-89% (2.03-fold), cPRA 90-97% candidates (2.62-fold), and cPRA 98-99.9% candidates (2.32-fold) in Era 3 vs. Era 1, but there were no statistically significant changes for cPRA 99.9%+ candidates. The net impact of these changes at the candidate level had different effects on HS recipients based on cPRA – such that DDKT was used less frequently over time for cPRA 80-89% recipients (80.1% in Era 3 vs. 86.2% in Era 1), but more frequently for cPRA 98-99.9% (95.8% vs. 78.7%) and cPRA 99.9%+ (96.2% vs. 59.1%) recipients. In contrast, KPD was used more frequently over time for cPRA 80-89% (8.6% in Era 3 vs. 3.8% in Era 1) and 90-97% recipients (5.9% vs. 4.2%), but less frequently for cPRA 98-99.9% (2.1% vs. 4.8%) and cPRA 99.9%+ (2.0% vs. 10.0%) recipients. Moreover, this decrease in non-KPD LDKT use in cPRA 98%+ recipients appears to be a driven by a direct decrease in utilization of this modality, since one-third fewer recipients used non-KPD LDKT in Era 3 as would have been expected given candidate characteristics (O:E for cPRA 98-99.9%+ candidates: 0.67). Although KAS has led to substantially higher DDKT rates for most HS candidates, this may have inadvertently led to decreased use of non-KPD LDKT to transplant cPRA 98%+ candidates.

Our findings of an increased likelihood of DDKT for cPRA 90%+ candidates, and decreased likelihood for cPRA 80-89% candidates, are consistent with a number of studies that have described

the impact of KAS on DDKT rates for the HS.[10-13, 50] However, we have extended this work by using national data to quantify changes in likelihood of KPD and non-KPD LDKT, which were not addressed in those studies. Our findings of increased likelihood of KPD for most HS candidates in the era of large, single- and multi-center KPD clearinghouses are also consistent with simulation data that showed more HS candidates would be able to find a KPD match with increasing registry size.[51] However, we extended this work by studying trends over the last decade (of which KAS is just one era), and by also quantifying how the net impact of these changes resulted in different trends in transplant modalities being used by HS recipients based on cPRA. While cPRA 80-89% recipients were less likely to have received DDKT, and more likely to have received LDKT, the opposite was true for cPRA 98%+ recipients, who were more likely to receive DDKT and less likely to receive LDKT (3.4% of cPRA 99.9% recipients underwent LDKT in Era 3, compared to 38.0% in Era 1). This appears to be a driven by a direct decrease in utilization of this non-KPD LDKT, since one-third fewer recipients used non-KPD LDKT in Era 3 as would have been expected given candidate characteristics. Although KAS has undoubtedly helped some cPRA 98%+ candidates undergo DDKT who might not previously have been able to undergo transplant, our findings suggest that some cPRA 98%+ candidates are actually foregoing LDKT, which might require a complicated KPD match or desensitization to facilitate incompatible LDKT, in favor of DDKT, which has become substantially easier under KAS. Although not every cPRA 98%+ candidate has a potential living donor available, it is possible that some of these candidates might benefit from KPD or incompatible LDKT.

This decrease in non-KPD LDKT use by cPRA 98%+ recipients might be concerning for two reasons. First, mortality and graft loss is significantly lower after compatible LDKT than after DDKT, and thus these candidates might be better served attempting to find a compatible match, such as through KPD [52]. Second, even if a candidate cannot find a compatible living donor, incompatible LDKT is associated with a survival benefit compared to waiting for DDKT.[24]

Moreover, some candidates are able to find a 'less incompatible' match by combining incompatible LDKT with KPD.[53, 54] However, incompatible LDKT is possibly associated with higher costs and more complications than compatible LDKT, and thus might not be appropriate for every cPRA 98%+ candidate with an incompatible living donor.[55-58] Nevertheless, beyond a direct benefit to the cPRA 98% recipient, increasing LDKT utilization would allow candidates without a living donor to undergo DDKT, thus increasing the number of patients able to benefit from kidney transplantation. One potential strategy to mitigate this decrease in the use of non-KPD LDKT might be to delay the awarding of priority points for cPRA 98%+ candidates until, for example, one year after waitlist registration. This might encourage candidates and centers to aggressively search for a living donor and, if necessary, provide sufficient time to find a compatible or 'less incompatible' match through KPD. Such a policy might resemble the recent policy change that created a phase-in period for exception points for liver transplant candidates with hepatocellular carcinoma, which has led to more balanced transplant rates between candidates with and without hepatocellular carcinoma, without an increase in waitlist mortality.[59]

Several limitations of our study are worth considering. First, not every HS DDKT candidate has a living donor available to them, and our estimates of likelihood of KPD and non-KPD LDKT cannot distinguish between candidates who had a potential living donor and those who did not. The OPTN does not collect data on whether transplant recipients had a potential living donor, nor on whether they received desensitization. However, the O:E ratios we calculated attempted to address this issue indirectly by determining how many candidates *would be expected* to undergo non-KPD LDKT in Era 3, if non-KPD LDKT was used for similar candidates in Era 3 as it had been for Era 1. Additionally, it is likely that there are between-center differences in how unacceptable antigens are determined and managed, details of which are not captured by the OPTN. Despite these limitations, the major strength of our study is our use of national registry data, which allows us to characterize trends in transplant modality usage at all centers in the country.

In conclusion, we found that the likelihood of DDKT and KPD increased for HS candidates over time, although the likelihood of non-KPD LDKT decreased. Moreover, we found that the net impact of these changes varied across cPRA, such that DDKT was used less frequently over time for cPRA 80-89% recipients, but more frequently for cPRA 98%+ recipients. In contrast, KPD was used more frequently over time for cPRA 80-97% recipients, but less frequently for cPRA 98%+ recipients. Additionally, this decrease in non-KPD LDKT appears to be the result of these candidates undergoing other transplant types instead, since one-third fewer recipients underwent non-KPD LDKT in Era 3 as would have been expected given candidate characteristics. One possible strategy to mitigate this decline might be to delay the awarding of priority points for DDKT until a specific time point after waitlist registration, in order to encourage the identification and utilization of potential living donors.

Table 1. Characteristics of highly sensitized candidates, by era of listing.

Characteristic	Era 1 (n=14,595)	Era 2 (n=13,487)	Era 3 (n=11,825)	p-value
Age (years), mean (SD)	48.4 (13.0)	49.4 (13.0)	49.7 (12.9)	<0.001
Female sex, %	36.3	35.8	34.0	<0.001
Race, %				<0.001
White	41.2	38.6	37.5	
Black	36.3	36.4	36.1	
Other	22.4	25	26.4	
Cause of ESRD, %				<0.001
Glomerular Diseases	27.8	28.1	28.4	
Diabetes	23.5	25.3	26.6	
Hypertension	24	22.7	20.9	
Polycystic Kidney Disease	6.5	6.9	7.1	
Other	18.2	17.0	17.0	
Blood Type, %				0.41
O	49.4	48.7	48.7	
A	32.1	32.2	32.7	
B	14.8	15.5	14.6	
AB	3.7	3.7	3.9	
cPRA (%), median (IQR)	92.0 (86.0, 98.0)	93.0 (86.0, 99.0)	94.0 (86.0, 99.0)	<0.001
Estimated post-transplant survival score, mean (SD)	49.5 (28.8)	50.9 (29.0)	49.7 (28.8)	<0.001
Years on dialysis, median (IQR)	2.5 (0.9, 5.2)	2.2 (0.7, 4.9)	1.8 (0.4, 4.2)	<0.001
History of prior transplant	48.3	47.0	44.0	<0.001
Prior living donor transplant, % of those with a prior transplant	36.2	36.2	39.1	

cPRA; calculated panel reactive antibody; ESRD, end-stage renal disease; IQR, interquartile range;

SD, standard deviation.

Table 2. Characteristics of HS recipients, by era of transplant.

Characteristic	Era 1 (n=5,098)	Era 2 (n=5,331)	Era 3 (n=8,374)	p-value
Recipient				
Age (years), mean (SD)	48.6 (13.0)	49.2 (13.1)	49.3 (12.8)	0.02
Female sex, %	65.2	63.7	64.6	0.3
Race, %				<0.001
White	48.5	47.6	41.3	
Black	31.0	29.7	31.6	
Other	20.5	22.8	27.1	
Cause of ESRD, %				0.5
Glomerular Diseases	32.3	32.7	33.5	
Diabetes	17.6	17.9	18.0	
Hypertension	21.2	20.7	21.2	
Polycystic Kidney Disease	8.1	8.5	8.0	
Other	20.8	20.3	19.3	
Blood Type, %				0.002
O	48.5	47.7	51.1	
A	36.6	36.7	33.9	
B	11.1	11.4	11.2	
AB	3.8	4.2	3.9	
cPRA (%)				<0.001
80-89	41.0	39.1	17.6	
90-97	37.5	38.3	25.7	
98-99.9	18.7	19.6	43.6	
99.9%+	2.8	3.1	13.1	
DDKT Sharing, %				<0.001
Local	61.6	64.3	39.0	
Regional	6.2	6.7	17.7	
National	32.2	29.0	43.3	
Years on dialysis, median (IQR)	3.5 (1.5, 6.5)	3.6 (1.4, 6.7)	3.9 (1.5, 7.3)	<0.001
History of a prior transplant, %	46.9	50.0	52.6	<0.001
Prior living donor transplant, % of those with a prior transplant	39.0	42.3	41.3	

cPRA; calculated panel reactive antibody; DDKT, deceased donor kidney transplant; ESRD, end-stage renal disease; IQR, interquartile range; SD, standard deviation.

Table 3. Likelihood of different transplant modalities among HS candidates by era and cPRA category.

	aSHR		
	Era 2 vs. Era 1*	Era 3 vs. Era 1*	Era 3 vs. Era 2*
Overall			
DDKT	0.97 1.04 1.12	**1.74 1.85 1.97**	**1.67 1.77 1.89**
LDKT	0.86 1.00 1.16	0.99 1.13 1.30	0.99 1.13 1.30
Non-KPD	**0.65 0.78 0.94**	**0.69 0.82 0.97**	0.87 1.04 1.25
KPD	**1.31 1.73 2.29**	**1.70 2.20 2.84**	**1.02 1.27 1.57**
cPRA			
80-89%			
DDKT	0.94 1.03 1.15	**0.76 0.84 0.92**	**0.73 0.81 0.89**
LDKT	0.71 0.89 1.11	**1.05 1.27 1.53**	**1.16 1.43 1.76**
Non-KPD	**0.54 0.70 0.92**	0.83 1.04 1.31	**1.14 1.49 1.93**
KPD	**1.02 1.53 2.29**	**1.41 2.03 2.91**	0.95 1.33 1.85
90-97%			
DDKT	0.95 1.07 1.22	**1.75 1.95 2.17**	**1.64 1.82 2.02**
LDKT	0.92 1.18 1.52	0.98 1.24 1.58	0.84 1.05 1.32
Non-KPD	0.67 0.92 1.25	0.58 0.78 1.07	0.62 0.85 1.17
KPD	**1.25 1.98 3.13**	**1.71 2.62 4.00**	0.94 1.32 1.86
98-99.9%			
DDKT	0.96 1.20 1.49	**5.57 6.62 7.85**	**4.71 5.52 6.48**
LDKT	0.80 1.15 1.65	0.63 0.91 1.31	0.56 0.79 1.13
Non-KPD	0.59 0.90 1.39	**0.37 0.58 0.92**	0.40 0.64 1.03
KPD	**1.05 2.21 4.66**	**1.14 2.32 4.73**	0.61 1.05 1.81
99.9%+			
DDKT	0.38 0.70 1.31	**4.23 6.49 9.96**	**5.73 9.24 14.90**
LDKT	0.47 1.31 3.67	0.35 0.95 2.59	0.30 0.73 1.73
Non-KPD	0.36 1.28 4.54	0.21 0.77 2.79	0.19 0.60 1.85
KPD	0.24 1.37 7.99	0.27 1.33 6.68	0.24 0.97 3.93

Bold indicates $p<0.05$

*Indicates reference group

aSHR, adjusted subhazard ratio; cPRA, calculated panel reactive antibody, DDKT, deceased donor kidney transplantation; KPD, kidney-paired donation; LDKT, living donor kidney transplantation.

Table 4. 3-year cumulative incidence of overall transplant for HS candidates by era and cPRA.*

cPRA	Era 1	Era 2	Era 3
80-89% (%)	48.5	50.2	46.2
90-97% (%)	32.0	34.1	47.9
98-99.9% (%)	13.1	16.5	50.1
99.9%+ (%)	5.2	5.1	27.0

*Includes all modalities (i.e. DDKT and overall LDKT)

cPRA, calculated panel reactive antibody.

Over time, there was a substantial increase in the percent of cPRA 90%+ candidates receiving a transplant by three years after listing. For example, 50.1% of cPRA 98-99.9% candidates received a transplant within three years in Era 3, compared to 13.1% in Era 1.

Table 5. Temporal trends in transplant modalities received by HS recipients by era and cPRA.

	Era 1	Era 2	Era 3	p-value
Overall (%)				
DDKT	84.1	86.4	91.0	<0.001
LDKT	15.9	13.6	9.0	
Non-KPD	11.6	7.5	4.8	
KPD	4.3	6.1	4.2	
cPRA				
80-89% (%)				
DDKT	86.2	89.7	80.1	<0.001
LDKT	13.8	10.3	19.9	
Non-KPD	10.0	6.2	11.3	
KPD	3.8	4.1	8.6	
90-97% (%)				
DDKT	86.0	86.5	87.7	<0.001
LDKT	14.0	13.5	12.3	
Non-KPD	9.8	7.3	6.4	
KPD	4.2	6.2	5.9	
98-99.9% (%)				
DDKT	78.7	82.0	95.8	<0.001
LDKT	21.3	18.0	4.2	
Non-KPD	16.5	8.6	2.1	
KPD	4.8	9.4	2.1	
99.9%+ (%)				
DDKT	59.1	68.7	96.2	<0.001
LDKT	40.9	31.3	3.8	
Non-KPD	30.9	20.1	1.9	
KPD	10.0	11.2	2.0	

cPRA, calculated panel reactive antibody; DDKT, deceased donor kidney transplantation; KPD, kidney-paired donation; LDKT, living donor kidney transplantation.

Table 6. Observed to expected ratios for HS recipients undergoing non-KPD LDKT, by era and cPRA.

	Observed	Expected	O:E	95% CI
Overall				
Era 1	277	277	Ref	-
Era 2	208	262	0.79	0.69-0.91
Era 3	281	258	1.09	0.97-1.22
cPRA				
80-89%				
Era 1	144	144	Ref	-
Era 2	86	127	0.68	0.54-0.84
Era 3	165	124	1.33	1.14-1.55
90-97%				
Era 1	85	85	Ref	-
Era 2	76	85	0.89	0.70-1.11
Era 3	78	81	0.96	0.76-1.20
98-99.9%				
Era 1	44	44	Ref	-
Era 2	40	45	0.89	0.63-1.21
Era 3	32	48	0.67	0.46-0.94
99.9%+				
Era 1	4	4	Ref	-
Era 2	6	5	1.20	0.44-2.61
Era 3	6	5	1.20	0.44-2.61

O:E. observed to expected ratio; CI, confidence interval.

Although this analysis was motivated by initial results in the cPRA 98-99.9% subpopulation, we have provided results for all cPRA groups. cPRA 98-99.9% candidates were approximately one-third less likely to undergo non-KPD LDKT in Era 3 as would be expected given candidate characteristics.

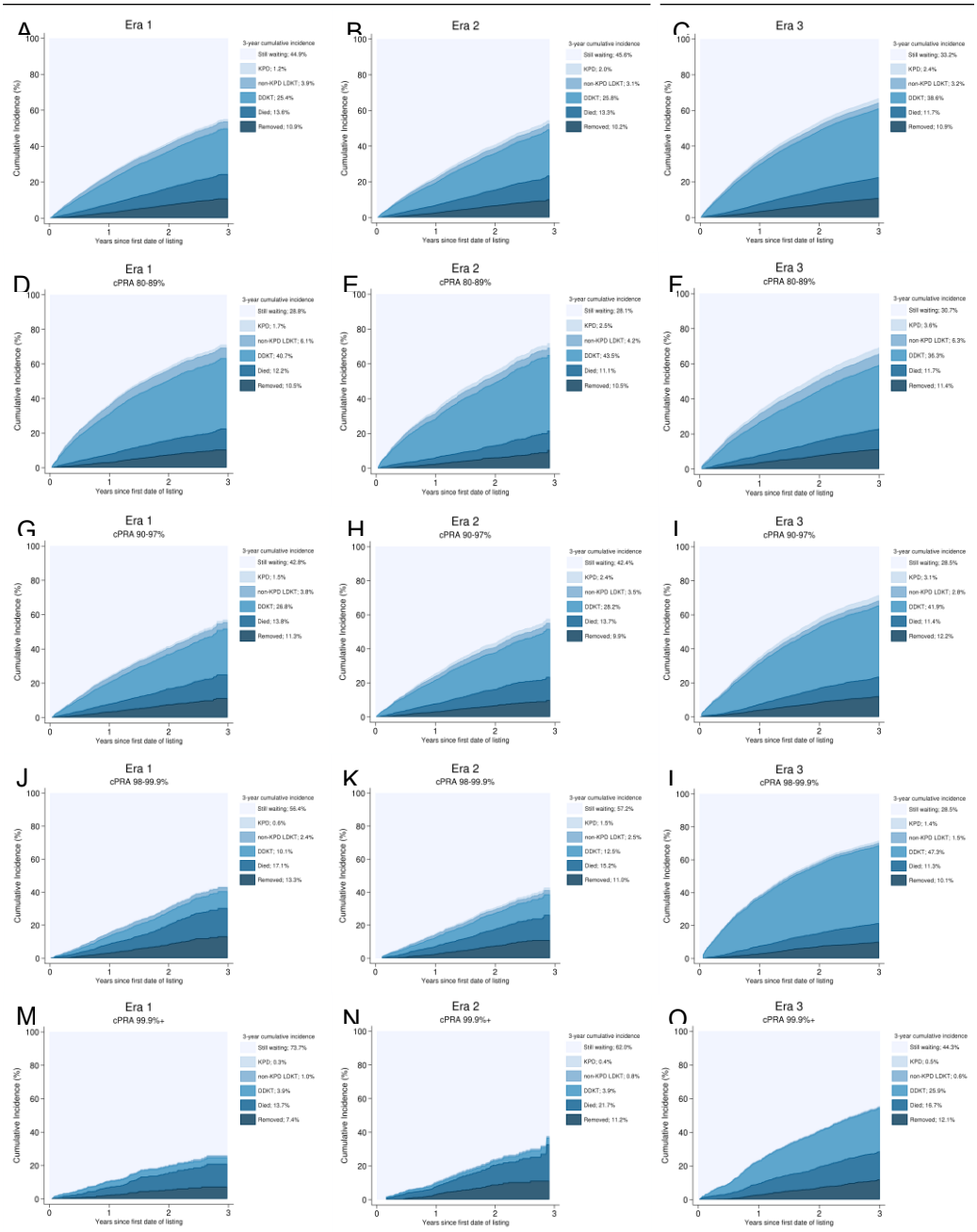
Table 7. Temporal trends in transplant modalities received by HS recipients by era and cPRA using alternative cPRA categorization

cPRA	Era 1	Era 2	Era 3	p-value
80.00-89.00%				
DDKT	86.2	89.6	80.4	<0.001
LDKT	13.8	10.4	19.6	
Non-KPD	10.0	6.2	11.2	
KPD	3.8	4.2	8.4	
90.00-97.49%				
DDKT	86.0	86.4	87.8	<0.001
LDKT	14.0	13.6	12.2	
Non-KPD	9.8	7.4	6.2	
KPD	4.2	6.2	5.9	
97.50-98.49%				
DDKT	78.2	86.2	88.0	<0.001
LDKT	21.8	13.8	12.0	
Non-KPD	15.7	7.2	6.9	
KPD	6.1	6.6	5.1	
98.50%-99.49%				
DDKT	80.3	79.3	93.8	<0.001
LDKT	19.7	20.7	6.2	
Non-KPD	16.2	9.3	3.0	
KPD	3.5	11.4	3.2	
99.50%+				
DDKT	71.2	77.4	97.9	<0.001
LDKT	28.8	22.6	2.1	
Non-KPD	22.3	12.8	0.9	
KPD	6.5	9.8	1.2	

cPRA, calculated panel reactive antibody; DDKT, deceased donor kidney transplantation; KPD, kidney-paired donation; LDKT, living donor kidney transplantation.

This sensitivity analysis was consistent with our main analysis. A decreasing proportion of cPRA 98.5%+ recipients underwent non-KPD LDKT (0.9% in Era 3 vs. 22.3% in Era 1 for 99.5%+ recipients) and KPD (1.2% vs. 6.5% for cPRA 99.5%+ recipients).

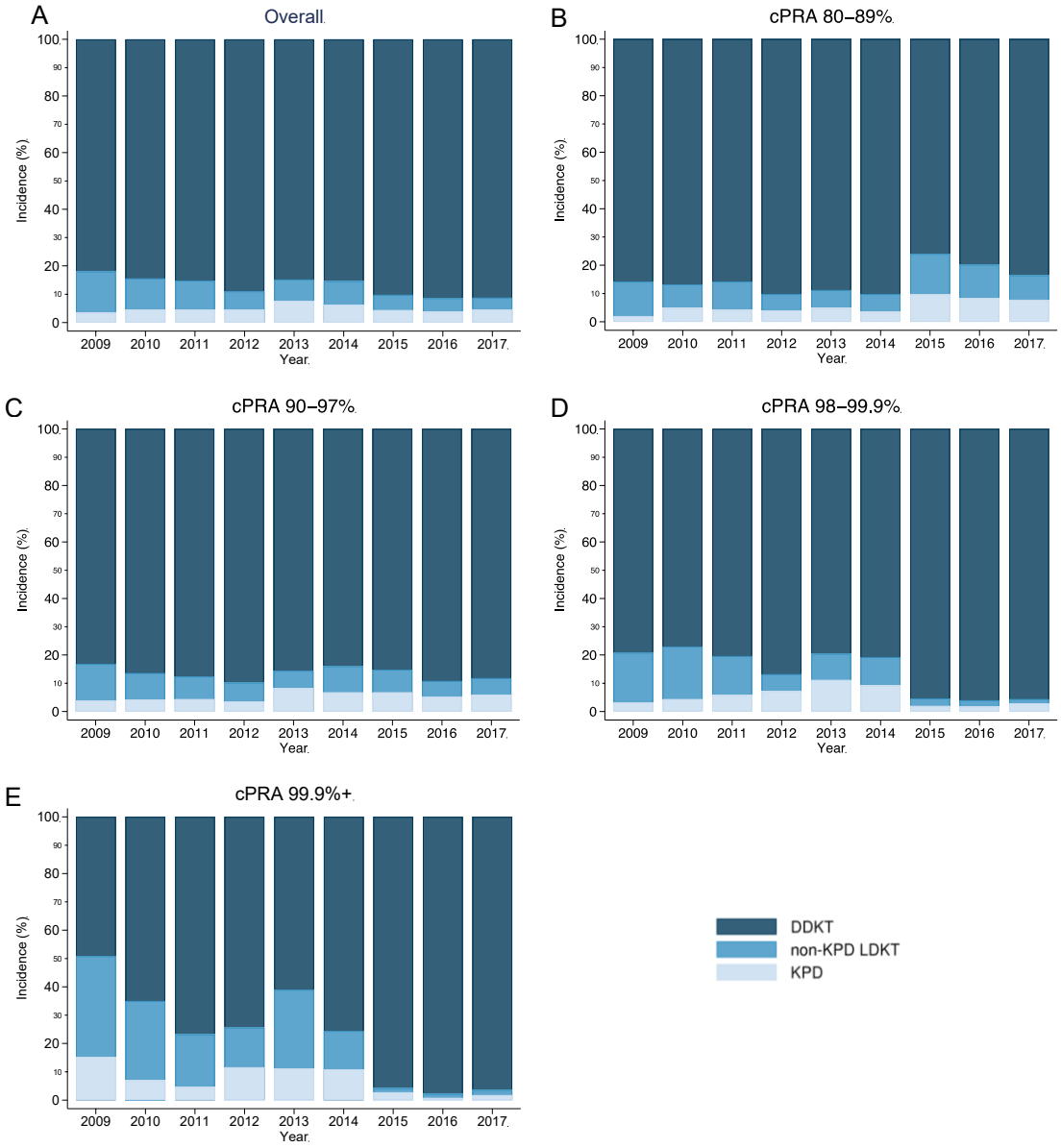
Figure 1. Outcomes of HS candidates by era and cPRA category



KPD, kidney-paired donation; LDKT, living donor kidney transplant; DDKT, deceased donor kidney transplant; KAS, Kidney Allocation System; Era 1: 1/1/2009-12/31/2011; Era 2: 1/1/2012-12/3/2014; Era 3: 12/4/2014-12/31/2017.

Each figure shows the crude cumulative incidence of each potential waitlist outcome at three-years after entering the DDKT waitlist by cPRA group (rows) and Era (columns).

Figure 2. Trends in highly sensitized recipient transplant modalities used by era and cPRA category.



Each figure (A-E) shows the annual percentage of HS recipients in each cPRA category that used each transplant modality. For example, 30.9% of cPRA 99.9%+ recipients underwent non-KPD LDKT in Era 1, which decreased to 20.1% in Era 2, and then to 1.9% in Era 3.

Chapter 4. Pediatric deceased donor kidney transplant outcomes under the Kidney Allocation System

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interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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ABSTRACT

The Kidney Allocation System (KAS) has resulted in fewer pediatric kidneys being allocated to pediatric deceased donor kidney transplant (pDDKT) recipients. This had prompted concerns that post-pDDKT outcomes may worsen. To study this, we used SRTR data to compare outcomes of 953 pre-KAS pDDKT (age<18 years) recipients (12/4/2012-12/3/2014) to 934 post-KAS pDDKT recipients (12/4/2014-12/3/2016). We analyzed mortality and graft loss using Cox regression, delayed graft function (DGF) using logistic regression, and length of stay (LoS) using negative binomial regression. Post-KAS recipients had longer pre-transplant dialysis times (median 1.26 vs. 1.07 years, p=0.02) and were more often cPRA 100% (2.0% vs. 0.1%, p=0.001). Post-KAS recipients had less graft loss than pre-KAS recipients (hazard ratio [HR]:$_{0.35}0.54_{0.83}$, p=0.005), but no statistically significant differences in mortality (HR:$_{0.29}0.72_{1.83}$, p=0.5), DGF (odds ratio [OR]:$_{0.93}1.32_{1.93}$, p=0.2), and LoS (LoS ratio:$_{0.96}1.06_{1.19}$, p=0.4). After adjusting for donor/recipient characteristics, there were no statistically significant post-KAS differences in mortality (adjusted HR [aHR]:$_{0.37}1.04_{2.92}$, p=0.9), DGF (adjusted OR:$_{0.94}1.41_{2.13}$, p=0.1), or LoS (adjusted LoS ratio:$_{0.93}1.04_{1.16}$, p=0.5). However, post-KAS pDDKT recipients still had less graft loss (aHR:$_{0.38}0.59_{0.91}$, p=0.02). KAS has had a mixed effect on short-term post-transplant outcomes for pDDKT recipients, although our results are limited by only two years of post-transplant follow-up.

INTRODUCTION

The Kidney Allocation System (KAS) was implemented on December 4, 2014, representing the largest change to deceased donor kidney allocation policy in the United States in over twenty years. The goals of KAS were to improve access to deceased donor kidney transplantation (DDKT) for historically disadvantaged groups (such as racial minorities and highly sensitized patients) and to better match the highest quality donor organs with recipients who have the longest expected post-transplant survival.[7] Except for regional and national sharing priority for highly sensitized candidates, pediatric recipients' place in the allocation sequence was not directly modified by KAS. However, a significant change was made to the method in which kidneys were allocated to them.[60] Prior to KAS, pediatric deceased donor kidney transplant (pDDKT) recipients were allocated kidneys under Share-35, whereby kidneys from donors less than 35 years old would be initially allocated to pDDKT.[61] Under KAS, pediatric candidates are now preferentially allocated kidneys with a Kidney Donor Profile Index (KDPI) < 35, representing a donor organ that is similar to the top 35% of kidneys recovered in the previous year. The goal of these changes was to maintain the pediatric priority for higher quality donor organs. Although early simulations suggested that pDDKT would remain unchanged after KAS implementation, changes in the allocation system can produce unintended consequences.[60, 62]

Early reports on the effect of KAS were encouraging, with studies showing an increase in transplantation rates for highly sensitized patients and African-American patients in the first year after KAS implementation, without a change in overall pDDKT rate.[13, 14] Nevertheless, a longer-term study showed that children < 6 years old were 21% less likely to undergo DDKT after KAS implementation.[15] Moreover, a recent report showed that pDDKT recipients < 10 years old experienced a 69% increase in the odds of delayed graft function (DGF) after KAS implementation, and recipients with DGF had a 2.2-fold increase in graft failure compared to those without DGF.[17]

Finally, another study showed that the overall percentage of pDDKT recipients that received a pediatric donor kidney decreased post-KAS.[16] These changes under KAS have prompted some concerns that KAS violates the ethical principles of utility (pediatric recipients are less frequently receiving high-quality kidneys from pediatric donors) and justice (decreased access to transplantation for pediatric candidates < 6 years old), and some have proposed modifications to KAS to attempt to reverse this change.[18, 19]

Before considering a change to allocation policy, we felt it was important to have a complete understanding of the effect of KAS on pDDKT recipients. To better inform this discussion, we explored whether KAS-related changes have led to worse post-transplant outcomes in pDDKT. We chose to study patient and graft survival, delayed graft function, and length of stay since these are important post-transplant outcomes for patients, families, and physicians, and could have been affected by KAS-related changes in donor/recipient case-mix. For example, a decrease in pediatric donors being allocated to pediatric recipients might lead to decreased graft survival, and an increase in highly sensitized recipients and recipients with a longer pre-transplant dialysis time might lead to an increased risk of DGF and longer LoS).[16, 17] Therefore, we analyzed national registry data to determine whether post-transplant outcomes (patient and graft survival, delayed graft function, and length of stay) for pDDKT recipients have worsened following KAS implementation. As a result of some of the negative consequences of KAS described above, we hypothesized that some of these post-transplant outcomes may have worsened under KAS.

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US,

submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[25] The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study population

We compared pDDKT (< 18 years old) recipients who were transplanted pre-KAS (12/4/2012 to 12/3/2014) to those transplanted post-KAS (12/4/2014 to 12/3/2016). This study was approved by the Johns Hopkins University Institutional Review Board.

Mortality and graft loss

We analyzed mortality and all-cause graft loss using Cox proportional hazards regression with a sandwich estimator, which accounts for clustering of outcomes by center.[26] We first used a univariable model, and then created a multivariable model, adjusting for the following recipient and donor factors: recipient age at transplant, gender, race/ethnicity, ABO blood type, years on dialysis, CPRA at transplant (0-19%, 20-94%, 95-100%), cause of end-stage renal disease (ESRD), donor age, cold ischemia time (CIT) in hours, KDPI (as a binary variable greater or less than 35%), organ share type (local, regional, or national), and receipt of a zero-mismatch organ. To analyze mortality, we administratively censored the pre-KAS cohort on 5/31/2015 and the post-KAS cohort on 5/31/2017, to ensure equal follow-up times between groups. We censored both cohorts at an earlier date for analysis of graft loss, since ascertainment of graft loss in SRTR lags behind that of mortality (pre-KAS cohort on 01/01/2015 and the post-KAS cohort on 01/01/2017).

Trends in graft loss

To determine if our results were due to secular trends in graft loss, we included additional groups of pDDKT recipients who were transplanted from 12/4/2006 to 12/3/2008, 12/4/2008 to 12/3/2010,

and 12/4/2010 to 12/3/2012. We administratively censored these groups on 01/01/2009, 01/01/2011, and 01/01/2013, respectively, to ensure equal follow-up time to the pre-KAS and post-KAS cohort. We then included a continuous time variable in our regression model to determine whether there were any secular trends in graft loss during the study period.

Delayed graft function and length of stay

We also examined changes in the incidence of DGF and LoS following KAS implementation. DGF was defined as the need for dialysis within the first week after transplantation, as reported to the OPTN. We analyzed DGF using logistic regression, excluding those who received a pre-emptive transplant (448 patients, or 23.7% of the original cohort). We analyzed LoS using negative binomial regression, excluding patients for whom their index hospitalization LoS was missing (65 patients, or 3.4% of the original cohort). We included a sandwich estimator in both models to account for within center clustering of outcomes.[26] Both DGF and LoS were first analyzed with a univariable model, then a multivariable model adjusting for the same donor and recipient characteristics as for graft loss and mortality.

Effect modifiers of graft loss

In our primary analysis, we found that post-KAS recipients had less graft loss than pre-KAS recipients. In order to understand post-KAS changes that may have resulted in this, we explored potential effect modifiers using interaction terms, with a separate unadjusted model for each interaction. Interactions between the donor and recipient characteristics used in our multivariable model were explored.

Sensitivity Analyses

Since prior studies have shown that younger recipients may have been uniquely disadvantaged by KAS, we also separately examined post-transplant outcomes among recipients < 6 years old and < 10

years old as a sensitivity analysis.[63] Additionally, we performed a sensitivity analysis for the development of DGF including pre-emptive pDDKT recipients, as they comprised almost 25% of our initial sample population.

Statistical analysis

We used the Wilcoxon rank-sum test to compare baseline differences in age, years on dialysis, CIT, and KDPI. We used Pearson's Chi-squared test or Fisher's exact test to compare baseline differences in other categorical variables as appropriate. Data was missing for 2.8% of our study population. We used Little's test to determine whether our data was missing completely at random. This test was non-significant, suggesting that the assumption that our data was missing completely at random was reasonable. Therefore, we performed complete case analysis for our adjusted regressions, where observations with missing data were excluded. Confidence intervals are reported as per the method of Louis and Zeger.[28] All analyses were performed using Stata 14.1/MP for Windows (College Station, Texas).

RESULTS

Study Population

Pre-KAS and post-KAS recipients were a similar age (median 13 years vs. 13, p=0.8) and were equally likely to be female (41.9% vs. 43.3%, p=0.5), white (38.4% vs. 40.6%, p=0.4), blood type O, (50.7% vs. 51.0%, p=0.7), have congenital anomalies of kidney and urinary tract as the cause of ESRD (29.3% vs. 29.7%, p=0.6), and receive nationally shared kidneys (4.2% vs. 4.1%, p=0.7) (Table 1). Post-KAS recipients spent more time on dialysis (median 1.26 years vs. 1.07, p=0.02), were more likely to have 100% CPRA (2.0% vs. 0.1%, p=0.001), and were equally like to have ≤ 3 mismatches with their donor (17.1% vs. 16.1%, p=0.5). Donor age increased slightly post-KAS (median [IQR] 22 years [18 – 29] vs. 22 years [17 - 27], p<0.001), and post-KAS recipients were less likely to receive an

organ from a pediatric donor (22.6% vs. 28.1%, p<0.01). CIT was not significantly different between groups (median 11.6 hours vs. 11.5 hours, p=0.3), nor was KDPI (median 12 vs. 11, p=0.4).

Graft loss

The cumulative incidence of graft loss at 2-years post-transplantation was 10.2% for pre-KAS recipients and 4.2% for post-KAS recipients, after a median follow-up time of 1.03 years (Figure 1). Through 2-years post-transplant, the unadjusted hazard of graft loss was lower for post-KAS recipients compared to pre-KAS recipients (hazard ratio [HR]: $_{0.35}0.54_{0.83}$, p=0.005; Table 2). However, there was no statistically significant post-KAS difference in graft loss for recipients < 10 years old (HR: $_{0.35}0.78_{1.70}$, p=0.5), or for recipients < 6 years old (HR: $_{0.15}0.44_{1.30}$, p=0.1).

In order to determine whether there were secular changes in graft loss preceeding KAS that could account for the post-KAS improvement in graft loss, we examined graft loss in recipients from successive two-year time periods preceding the pre-KAS group (2006-2008, 2008-2010, and 2010-2012). The cumulative incidence of graft loss at 2-years post-transplant was 11.2% for 2006-2008 recipients, 10.5% for 2008-2010 recipients, and 6.1% for 2010-2012 recipients (Figure 1). In our model adjusted for a continuous trend over time, there was no relationship between time and risk of graft loss (p=0.9), suggesting that there were no underlying secular trends responsible for the improved graft loss post-KAS.

In order to understand potential causes for this apparent decrease in graft loss in post-KAS recipients, we adjusted for donor and recipients characteristics, but this did not appreciably change our results (adjusted HR [aHR]: $_{0.38}0.59_{0.91}$, p=0.02; Table 2). None of the potential interaction terms between KAS and recipient and donor characteristics were significant.

Mortality

The cumulative incidence of mortality at 2-years post-transplantation was 1.1% for pre-KAS recipients and 0.6% for post-KAS recipients, after a median follow-up time of 1.47 years. Through 2-years post-transplantation, the unadjusted hazard of mortality was not significantly different between post-KAS recipients and pre-KAS recipients (HR: $_{0.29}0.72_{1.83}$, p=0.6; Table 2). This remained consistent after adjusting for donor and recipient characteristics (aHR: $_{0.37}1.04_{2.92}$, p=0.9; Table 2). There were no statistically significant post-KAS differences in mortality for recipients < 10 years old (HR: $_{0.28}0.97_{3.37}$, p=1.0) or < 6 years old (HR: $_{0.23}0.85_{3.07}$, p=0.8; Table 2).

Delayed Graft Function

Among patients who were not transplanted pre-emptively, 8.7% of pre-KAS recipients developed DGF compared to 11.1% of post-KAS recipients. Post-KAS recipients were not significantly more likely to develop DGF compared to pre-KAS recipients (odds ratio [OR]: $_{0.90}1.32_{1.93}$, p=0.2, Table 2). This remained consistent after adjusting for donor and recipient characteristics (adjusted OR: $_{0.94}1.41_{2.13}$, p=0.1; Table 2). There were no statistically significant differences in development of delayed graft function in recipients < 10 years old (OR: $_{0.67}1.28_{2.45}$, p=0.5) or for recipients < 6 years old (OR: $_{0.58}1.30_{2.95}$, p = 0.5). In our sensitivity analysis including pre-emptive pDDKT recipients, 6.9% of pre-KAS recipients developed DGF compared to 9.4% of all post-KAS recipients. These recipients were not significantly more likely to develop DGF post-KAS compared to pre-KAS ($_{0.95}1.40_{2.06}$, p=0.1). There were no statistically significant differences after adjusting for donor and recipient characteristics (adjusted OR: $_{0.98}1.49_{2.25}$, p=0.06).

Length of Stay

The median (IQR) length of stay for pre-KAS recipients was 8 days (6 - 11), and for post-KAS recipient it was 8 days (6 - 12). LoS for post-KAS recipients was not significantly different compared to pre-KAS recipients (LoS ratio: $_{0.94}1.06_{1.19}$, p=0.4, Table 2). This remained consistent after adjusting for donor and recipient characteristics (adjusted LoS ratio: $_{0.93}1.04_{1.16}$, p=0.5; Table 2). There were no

statistically significant differences in LoS for recipients < 10 years old (LoS ratio: $_{0.83}1.00_{1.21}$, p=1.0) or for recipients < 6 years old (LoS ratio: $_{0.80}0.98_{1.20}$, p=0.8).

DISCUSSION

In this national study of pDDKT recipients, we did not find any evidence that post-transplant mortality or LoS worsened in the first two years post-KAS. Although there was no statistically significant change in the incidence of DGF, our point estimate approached statistical significance despite a relatively small sample size. We also showed that graft loss decreased post-KAS, although this was not explained by any KAS-related changes in donor or recipient characteristics that we studied. Additionally, there were no underlying secular trends in graft loss during the study period that could account this improvement. We also did not observe any statistically significant worsening of outcomes in younger recipients, who have been shown to be specifically affected by KAS.[15, 17]

The implementation of KAS has led to many positive changes for the adult DDKT population. Sensitized patients, racial minorities, and certain blood types now have improved access to DDKT (6, 7, 17-23).[10-14, 20, 21, 64, 65] Nevertheless, one study in the pDDKT population showed that recipients are less likely to receive a pediatric kidney after KAS as a consequence of using KDPI to allocate kidneys, an index which does not fully capture the unique considerations of pediatric donors (low height and weight, characteristics such as en bloc vs. single graft) and may not accurately predict graft survival for pediatric recipients.[16, 66] The KDPI formula assigns higher scores to kidneys from younger, and consequentially smaller, donors. Therefore, kidneys from pediatric donors may be assigned a high KDPI that precludes allocation to pediatric recipients.[66] Although a decrease in allocation of pediatric kidneys to pDDKT recipients is concerning, our results suggest that this change has not led to worsened post-transplant graft survival. In contrast, we have shown that graft survival was actually improved in the two years post-KAS compared to the two years pre-KAS, in the

absence of any secular trends. One potential explanation for improved graft loss might be improved recipient selection, through mechanisms not currently measured in registry data. Additionally, an underlying change in management of pediatric recipients, unrelated to KAS, might also explain the improved two-year graft survival. However, to our knowledge there have been no recent large-scale changes in the management of pDDKT recipients whose effect would be stronger than the effect of KAS, which represents the largest change to the allocation system in almost two decades.

We also did not find any statistically significant changes in the incidence of DGF and LoS following pDDKT after KAS implementation. DGF is an important outcome to study since it is associated with worse post-transplant outcomes, including acute rejection and graft failure (25-28).[36, 67-69] Moreover, it is a relatively more common complication after DDKT, such that any differences in its incidence after KAS should be readily apparent. Our finding of no statistically significant difference in DGF rates after KAS is in contrast to a study that reported a 69% increase in the odds of DGF for pDDKT recipients < 10 years old.[17] This study included five years of pre-KAS recipients and two years of post-KAS recipients, focusing mainly on recipients < 10 years old. In contrast, we limited our pre-KAS cohort to only include two years of all pDDKT recipients, in order to increase its comparibility to our post-KAS cohort and limit the impact of any secular trends. As such, their study was more powered than ours was for the analysis of recipients < 10 years old, and might explain the difference in our findings. We did not find a statistically significant difference, in either overall or subgroup specific rates of DGF. Given our small sample size, it is possible that we were underpowered to detect a true difference of this size. However, in the context of an increase in DGF reported in the adult literature, the prior pediatric study suggesting an increased risk of DGF for recipients < 10 years old, and our results which approached statistical significance despite our small sample size, there may be a true increase in DGF rates for pDDKT recipients post-KAS that we are underpowered to detect in the current study. We also did not find a change in LoS for post-KAS recipients, which is consistent with a report from the adult literature.[70] This is reassuring given that

the mean pre-transplant dialysis time and the proportion of cPRA 100% recipients increased significantly in our study post-KAS, both of which are associated with higher rates of DGF and could potentially have increased LoS.[36, 69]

It has recently been suggested that KAS, as it stands now for pediatric patients, violates fundamental ethical principles, and that KAS should be modified to reverse some of the changes it instituted.[18, 19] This has been based on arguments for decreased justice (decreased access to transplantation for children < 6 years old) and utility (the highest quality pediatric donor kidneys are not being as frequently directed to children, who have the longest expected post-transplant survival).[19] Without question, critical appraisal of KAS is important, and an ongoing evaluation of how it is affecting pediatric candidates is necessary to ensure that pediatric candidates continue to receive relative prioritization. Our results add context to this discussion, and underscore that KAS has had a complex effect on the pediatric population. It has led to decreased DDKT rates for candidates < 6 years, a potentially increased incidence of DGF, but also decreased graft loss. As the transplant community grapples with whether, or how, to modify KAS for pediatric patients, our results add an understanding of how KAS has affected a range of post-transplant outcomes to these discussions. Although pre-transplant outcomes of pediatric candidates are outside of the scope of the current study (i.e. equity in access to DDKT), we felt it was important to study post-transplant outcomes of pediatric recipients, who are equally important stakeholders in, and equally affected by KAS. Ultimately, discussions of KAS modifications should consider the entire context of both pre-transplant and post-transplant changes for pediatric candidates.

Our study has several noteworthy limitations. In using national registry data, we depend on accurate outcome ascertainment. In pDDKT recipients, graft loss is a rare event and therefore inaccurate graft loss ascertainment could bias our results. However, we standardized follow-up times between pre-KAS and post-KAS recipients to minimize differences in ascertainment across the two eras. We are

also limited to only two years of follow-up after KAS implementation. The changes in outcomes (or lack thereof) we have demonstrated here may change over time, especially for longer-term outcomes such as patient and graft survival. Despite this, we feel it is important to document short-term trends, to identify any unintended consequences of KAS. Additionally, as with any observational study using national registry data, we are unable to account for factors not captured by SRTR that might influence post-transplant outcomes (i.e. unmeasured confounding). Finally, studies of pediatric transplant recipients are limited by small sample sizes, and lower statistical power, relative to studies of adult recipients, and our study is no exception. Although we did not find any statistically significant post-KAS differences in mortality or DGF, this does not necessarily mean that there have not been smaller changes (but clinically important) that we are underpowered to detect. Although there is no analytical technique to overcome this weakness, our results should be considered in the full context of our sample size, point estimates, confidence intervals, and p-values.

In conclusion, our results suggest that KAS has had a mixed effect on post-transplant outcomes for pDDKT recipients, although they should be considered in the context of a relatively small sample size and short-term follow-up. There were no statistically significant changes in mortality, LoS, or DGF. The small increase in the post-KAS incidence of DGF we report approached statistical significance, and in the context of other adult and pediatric literature, may represent a true increase in DGF post-KAS. Conversely, two-year graft survival was significantly improved post-KAS, although this was not adequately explained by changes in donor or recipient characteristics that we studied. Nevertheless, ongoing assessment of post-transplant outcomes should continue, to ensure that the highest-quality data is being used to critically evaluate the ongoing effects of KAS.

Table 1. Characteristics of pre-KAS recipients compared to post-KAS recipients.

	Pre-KAS N=953	Post-KAS N=934	p-value	Missingness (%)
Recipient Characteistics				
Age at tx, median (IQR)	13 (7, 16)	13 (7, 16)	0.8	0
Female	399 (41.87%)	404 (43.25%)	0.6	0
Race/ethnicity			0.4	0
White	366 (38.51%)	379 (40.58%)		
Hispanic	247 (25.92%)	209 (22.38%)		
African-American	38 (3.99%)	46 (4.93%)		
Asian	271 (28.33%)	269 (28.80%)		
Others	31 (3.25%)	31 (3.32%)		
Blood type			0.7	0
A	305 (32.00%)	314 (33.62%)		
B	124 (13.01%)	108 (11.56%)		
AB	41 (4.30%)	36 (3.85%)		
O	483 (50.68%)	476 (50.96%)		
Years on dialysis, median (IQR)	1.07 (0.06, 2.27)	1.26 (0.11, 2.63)	0.02	0.2
CPRA at tx			0.001	0
0-19%	789 (82.79%)	777 (83.19%)		
20-94%	151 (15.84%)	128 (13.70%)		
95-97%	8 (0.84%)	5 (0.54%)		
98%	2 (0.21%)	4 (0.43%)		
99%	2 (0.21%)	1 (0.11%)		
100%	1 (0.10%)	19 (2.03%)		
Diagnosis at transplant			0.6	0
CAKUT*	279 (29.28%)	277 (29.66%)		
Other familial/metabolic	59 (6.19%)	59 (6.32%)		
GN*	46 (4.83%)	32 (3.43%)		
Focal Glomerularsclerosis	113 (11.86%)	118 (12.63%)		
Other	456 (47.85%)	448 (47.97%)		
Donor Characteristics				
Age, median (IQR)	22 (17, 27)	22 (18, 29)	<0.001	0
Cold ischemia time in hours, median (IQR)	11.5 (8.0, 15.3)	11.6 (8.0, 16.3)	0.3	2.5
KDPI*, median (IQR)	11 (6, 22)	12 (6, 21)	0.4	0
Sharing			0.7	
Local	873 (91.61%)	863 (92.40%)		
Regional	40 (4.20%)	33 (3.53%)		
National	40 (4.20%)	38 (4.07%)		
HLA mismatches ≤ 3	163 (17.1%)	150 (16.1%)	0.5	0.05

* CAKUT, Congenital Anomalies of Kidney and Urinary Tract; GN, Glomerularonephritis; KDPI, Kidney Donor Profile Index, calculated using 2017 as the reference year.

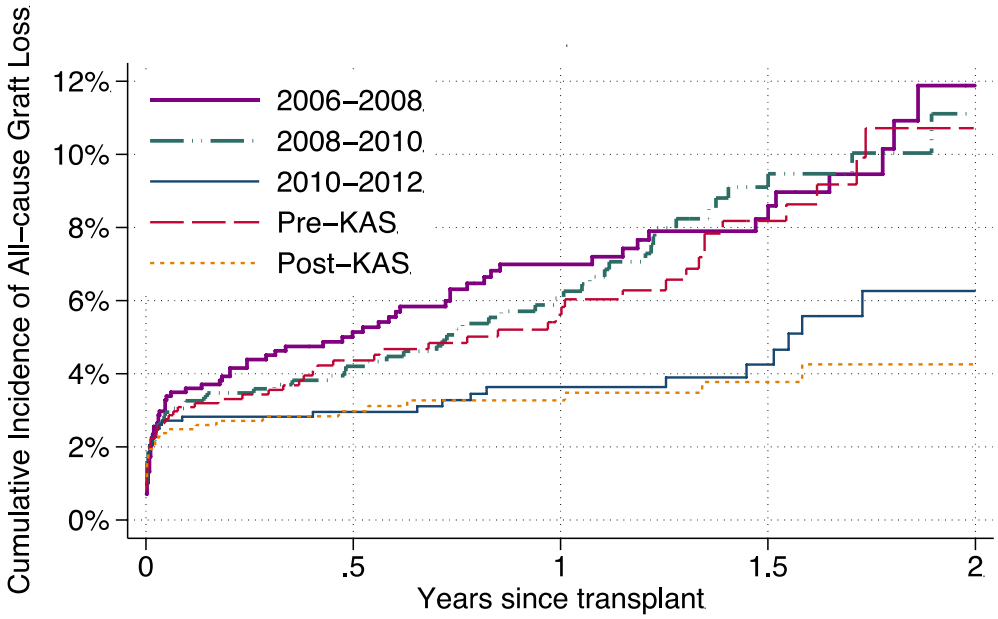
Table 2. Relative Risk of events post-KAS compared to pre-KAS. Proportional hazard Cox regressions were used for graft loss and patient mortality. Logistic regression was used for delayed graft function. Negative binomial regression was used for length of stay.

	Age<18	Age 10-17	Age<10	Age<6	Age<18 Adjusted
Graft loss (HR)	**$_{0.35}0.54_{0.83}$**	**$_{0.25}0.45_{0.81}$**	$_{0.35}0.78_{1.70}$	$_{0.15}0.44_{1.30}$	**$_{0.38}0.59_{0.91}$**
Patient mortality (HR)	$_{0.29}0.72_{1.83}$	$_{0.03}0.34_{3.99}$	$_{0.28}0.97_{3.37}$	$_{0.23}0.85_{3.07}$	$_{0.37}1.04_{2.92}$
DGF (OR)	$_{0.90}1.32_{1.93}$	$_{0.87}1.34_{2.07}$	$_{0.67}1.28_{2.45}$	$_{0.58}1.30_{2.95}$	$_{0.94}1.41_{2.13}$
LoS (LoS ratio)	$_{0.94}1.06_{1.19}$	$_{0.94}1.09_{1.25}$	$_{0.83}1.00_{1.21}$	$_{0.80}0.98_{1.20}$	$_{0.93}1.04_{1.16}$

HR, hazard ratio; OR, odds ratio; LoS, length of stay; DGF, delayed graft function

All ratios denote the increased or decreased risk for post-KAS recipients compared to pre-KAS recipients. Bolded values represent a ratio that significantly different than 1.0 ($p<0.05$). DGF results are with pre-emptive recipients excluded, although inferences remain the same with these recipients included.

Figure 1. All-cause graft loss by calender year. Each line represents recipients from five separate groups: recipients from 2006-2008, 2008-2010, 2010 - 2012, the pre-KAS cohort, and the post-KAS cohort. The cumulative incidence of graft loss was lowest in the post-KAS group.



Number at risk (Number of graft loss)

2006–2008	989	(48)	748	(12)	511	(5)	279	(6)	45
2008–2010	995	(40)	768	(12)	533	(13)	277	(3)	33
2010–2012	931	(27)	718	(4)	475	(2)	256	(4)	36
Pre–KAS	953	(39)	679	(7)	473	(9)	235	(4)	28
Post–KAS	934	(27)	720	(2)	481	(2)	263	(1)	20

Chapter 5. Changes in offer and acceptance patterns for pediatric kidney transplant candidates under the new Kidney Allocation System

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ABSTRACT

Stakeholders have expressed concerns regarding decreased deceased donor kidney transplant (DDKT) rates for pediatric candidates under KAS. To better understand what might be driving this, we studied SRTR kidney offer data for 3,642 pediatric (age<18) kidney-only transplant candidates between 12/31/2012-12/3/2014 (pre-KAS) and 12/4/2014-1/6/2017 (post-KAS). We used negative binomial regression and multilevel logistic regression to compare offer and acceptance rates pre- and post-KAS. We stratified by donor age (<18, 18-34, and 35+) and KDPI (<35% and ≥35%) to reflect differing allocation prioritization pre-KAS and post-KAS. As might be expected from prioritization changes, post-KAS candidates were less likely to receive offers for donors 18-34 years old with KDPI≥35% (adjusted incidence rate ratio [aIRR]: $_{0.18}0.21_{0.25}$, p<0.001), and more likely to receive offers for donors 18-34 years old and KDPI<35% (aIRR: $_{1.12}1.20_{1.29}$, p<0.001). However, offer acceptance practices also changed post-KAS: kidneys from donors 18-34 years old and KDPI<35% were 24% less likely to be accepted post-KAS (adjusted odds ratio: $_{0.61}0.77_{0.98}$, p=0.03). Using kidneys from donors 18-34 years old with KDPI<35% post-KAS to the same extent they were used pre-KAS might be an effective strategy to mitigate any decrease in DDKT rates for pediatric candidates.

INTRODUCTION

The Kidney Allocation System (KAS) implemented on December 4, 2014 was designed to better match deceased donor kidneys with the longest expected graft survival to patients expected to live the longest post-transplant ("longevity matching").[4, 7] Under KAS, the way in which kidneys were allocated to pediatric candidates was changed, in part to keep a standardized allocation system based on the Kidney Donor Profile Index (KDPI). Prior to KAS, pediatric candidates were preferentially allocated donors ≤35 years old; under KAS, they are preferentially allocated organs from donors with a KDPI<35%.[1] However, there have been several unintended changes for pediatric candidates under KAS.

One of these unintended changes has been a 21% decrease in deceased donor kidney transplant (DDKT) rates for candidates <6 years old.[15] Also, two studies have described a decrease in the number of pediatric recipients receiving organs from pediatric donors, with absolute decreases ranging from 3.3% - 11%.[16, 17] Furthermore, one study noted a 121 day increase in the amount of time recipients <10 years old spent on the waitlist prior to transplant after KAS, and an absolute 6.7% increase in the percentage of recipients waiting longer than one year for transplant.[17] However, the cause of these changes has yet to be established. One possibility is that KAS has directed organs that are well suited for pediatric candidates towards adult candidates, and thus pediatric candidates are no longer receiving the same high-quality offers they were before KAS. Alternatively, it may be that kidney acceptance practices have changed under KAS, and high-quality kidneys are being offered to pediatric candidates but not accepted. It would be useful to understand how any KAS-related changes in kidney offers or acceptance practices have contributed to these unintended consequences of KAS.

To better understand these observations, we studied how kidney offer and acceptance patterns have changed under KAS using national kidney offer data. Our goals were to (i) compare offers to pediatric candidates on the waitlist before and after KAS, (ii) compare acceptance patterns before and after KAS, (iii) determine how these offer and acceptance patterns varied across donor age and KDPI, and (iv) determine whether KAS-related changes differentially impacted the youngest pediatric candidates (<6 years old).

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR) December 2018 public release. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[25] The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. This study was approved by the Johns Hopkins University Institutional Review Board.

Study population

To characterize offer patterns on the waitlist, we studied 3,642 pediatric kidney-only transplant candidates (listed at age<18 years) who were ever active on the waitlist in the two years before (pre-KAS: 12/31/2012-12/3/2014) and after KAS (post-KAS: 12/4/2014-1/6/2017). To characterize offer acceptance, we studied 3,048 pediatric kidney transplant candidates who were ever offered a deceased donor kidney in the two years pre-KAS and post-KAS. Pediatric kidney transplant candidates who listed for liver transplantation during the study period were excluded (n=116).

Candidates who turned 18 while on the waitlist remained in our study, as they were still prioritized as pediatric candidates. We compared pediatric candidates actively listed pre- and post-KAS using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Candidates actively listed pre- and post-KAS were included in both columns of Table 1 and contribute person-time to each era.

Match-run data

Each time a deceased donor kidney becomes available, candidate and donor factors are input to generate an appropriate offer match-list, from which a kidney is offered to each candidate in turn based on the current allocation system and candidate priority. Match-run data includes a record of all offers made for each kidney, and whether the offer was declined or accepted. We excluded bypassed offers (offers made outside the formal match list using a bypass code; for example, donor medical urgency requiring immediate organ placement) and offers made for kidneys that were never accepted by anyone (i.e. discards). In addition, offers reported as accepted in the match-run data that did not have an associated transplant record were considered declines (n=7), and offers reported as declines in the match-run data that did have an associated transplant record were considered acceptances (n=95).

Offer rate

We calculated the offer rate, defined as the total number of offers made to pediatric candidates per total active person-years on the waitlist, pre- and post-KAS for all offers and for offers across donor age and KDPI. We stratified by donor age (categorized as <18, 18-34, and 35+) and KDPI (<35% and ≥35%) to reflect differing allocation prioritization pre- vs post-KAS. To determine whether the offer rate per person-year changed post-KAS and to account for overdispersion of offer counts, we used negative binomial regression with offer rate as the dependent variable and actively waitlisted time post-KAS as the primary exposure.[50, 71-73] We adjusted for candidate age, sex, race, primary

diagnosis, time on dialysis, preemptive listing, and cPRA (calculated panel reactive antibody, modeled as 0%, 1-79%, and 80%+), and stratified by donor age (<18, 18-34, 35+ yo) and KDPI (<35% vs ≥35%).

Offer acceptance

We calculated the percent of offers that were accepted pre- and post-KAS for all offers and for offers within each donor age and KDPI stratum. To determine whether offer acceptance changed post-KAS, we used multilevel logistic regression with offer acceptance as the dependent variable and offer made post-KAS as the primary exposure. We adjusted for candidate age, sex, race, primary diagnosis, time on dialysis, preemptive listing, cPRA, and calendar time, and stratified by donor age (<18, 18-34, and 35+) and donor KDPI (<35% vs. ≥35%). We used logistic regression to model the binary outcome of offer acceptance, and the multilevel framework with a random for transplant center allowed us to account for potential within-center clustering and between-center differences in acceptance practices.[74]

Accepted and declined kidneys

To identify changes in the deceased donor kidneys that were accepted or declined post-KAS, we compared the clinical and demographic characteristics of accepted and declined deceased donors pre- and post-KAS using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous non-parametric variables. Kidneys from the same donor were only included once in Table 4.

Statistical analysis

Confidence intervals are reported as per the method of Louis and Zeger.[28] A 2-sided α level of 0.05 was used to indicate statistical significance. All analyses were performed using Stata 15 (College Station, Texas).

RESULTS

Pediatric candidates pre- and post-KAS

There were 2,137 and 2,095 pediatric candidates actively listed in the pre- and post-KAS eras. Characteristics of pediatric candidates on the kidney transplant waitlist remained largely unchanged between eras (Table 1); pre- and post-KAS median age at study entry was 13 (interquartile range [IQR] 8-16, p=0.9), 59.2% vs 58.1% were male (p=0.5), 25.5% vs 22.9% were black/African-American (p=0.1), and 30.9% vs 29.6% were listed preemptively (p=0.4).

Offers pre- and post-KAS

In the two years pre-KAS, 8,240 offers were made to active pediatric candidates. Pre-KAS, 24.5% of offers were from donors <18 years old, 68.6% from donors 18-34 years old, 6.9% from donors 35+ years old, and 69.9% from donors with KDPI<35% (Figure 1A, left panel). In the two years post-KAS, 9,953 offers were made to active pediatric candidates. Post-KAS, 11.6% were from donors <18 years old, 68.8% from donors 18-34 years old, 19.6% from donors 35+ years old, and 88.8% from donors with KDPI<35% (Figure 1A, right panel). The percent of offers from donors <18 years old with KDPI≥35% decreased from 13.1% pre-KAS to 2.4% post-KAS (Figure 1).

Offer rates per person-year pre- and post-KAS

Among actively listed pediatric candidates, 76.9% pre-KAS vs 82.8% post-KAS were ever offered a deceased donor kidney that was eventually accepted by someone (p<0.001). More specifically, 25.4% vs 28.1% were ever offered a kidney from a donor <18 years old with KDPI<35% (p=0.045), 24.6% vs 8.0% were ever offered a kidney from a donor <18 years old with KDPI≥35% (p<0.001), 62.9% vs 70.5% were ever offered a kidney from a donor 18-34 years old with KDPI<35% (p<0.001), 23.0% vs 8.9% were ever offered a kidney from a donor 18-34 years old with KDPI≥35% (p<0.001),

5.7% vs 32.2% were ever offered a kidney from a donor >35 years old with KDPI<35% (p<0.001), and 12.3% vs 18.8% were ever offered a kidney from a donor ≥35 years old with KDPI≥35%.

Accounting for person-time, the crude offer rate overall increased from 7.5 offers per waitlist-year pre-KAS to 9.0 post-KAS (p<0.001, Table 2). The crude offer rate for kidneys from donors <18 years old with KDPI<35% remained similar at 0.81 pre-KAS and 0.82 post-KAS (p=0.2), whereas the crude offer rate for kidneys from donors <18 years old with KDPI≥35% decreased from 0.95 to 0.22 (p<0.001). After adjustment, the overall offer rate increased post-KAS by 13% (adjusted incidence rate ratio [aIRR]: $_{1.01}1.08_{1.15}$, p=0.02) (Table 2). However, the association between KAS and offer rates varied across donor age and KDPI. Offer rates for kidneys from donors <18 years old and KDPI<35% did not significantly change (aIRR: $_{0.78}0.88_{1.00}$, p=0.04), whereas offer rates for those with KDPI≥35% decreased by 79% post-KAS (aIRR: $_{0.18}0.21_{0.25}$, p<0.001). Offer rates for kidneys from donors 18-34 years old and KDPI<35% increased by 27% post-KAS (aIRR: $_{1.12}1.20_{1.29}$, p<0.001), whereas offer rates for those with KDPI≥35% decreased by 79% post-KAS (aIRR: $_{0.17}0.21_{0.25}$, p<0.001). Offer rates for kidneys from donors 35+ years old and KDPI<35% increased substantially post-KAS (aIRR: $_{7.09}8.57_{10.37}$, p<0.001), as did offer rates for those with KDPI≥35% (aIRR: $_{1.21}1.43_{1.69}$, p<0.001).

Offer acceptance pre- and post-KAS

Pre-KAS, 12.2% (n=1002 transplants) of deceased donor kidneys offers were accepted versus 10.6% (n=1053 transplants) post-KAS. Overall, this change was not statistically significant (adjusted odds ratio [aOR]: $_{0.76}0.95_{1.18}$, p=0.6); however, the percent of offers accepted pre- versus post-KAS varied by donor age and KDPI (Table 3). After adjustment, kidneys from donors <18 years old and KDPI<35% were equally likely to be accepted post-KAS (aOR: $_{0.77}1.06_{1.45}$, p=0.8; absolute acceptance 21.8% pre-KAS vs. 22.1% post-KAS), as were those with KDPI≥35% (aOR: $_{0.30}0.65_{1.40}$, p=0.2; absolute acceptance 5.4% pre-KAS vs. 3.8% post-KAS). In contrast, kidneys from donors 18-

34 years old and KDPI<35% were 23% less likely to be accepted post-KAS (aOR: $_{0.61}0.77_{0.98}$, p=0.03; absolute acceptance 14.2% pre-KAS vs. 10.4% post-KAS). Kidneys from donors 18-34 years old and KDPI≥35% were equally likely to be accepted post-KAS (aOR: $_{0.57}1.07_{2.01}$, p=0.8; absolute acceptance 5.9% pre-KAS vs. 8.6% post-KAS). Kidneys from donors 35+ years old with KDPI<35% were substantially more likely to be accepted post-KAS (aOR: $_{1.16}2.82_{6.87}$, p=0.02; absolute acceptance 4.4% pre-KAS vs. 8.4% post-KAS), although those with KDPI≥35% were equally likely to be accepted post-KAS (aOR: $_{0.75}1.68_{3.74}$, p=0.2; absolute acceptance 2.3% pre-KAS vs. 3.6% post-KAS).

Accepted and declined kidney characteristics pre- and post-KAS

There were 1,002 kidneys (878 donors) accepted by pediatric candidates pre-KAS, and 1,053 kidneys (884 donors) accepted post-KAS. Compared to kidneys pre-KAS, those accepted post-KAS were less likely to be from donors <18 years old (26.2% pre-KAS vs 19.6% post-KAS, p<0.001), and more likely to be at PHS increased infectious risk (8.0% pre-KAS vs 13.6% post-KAS, p<0.001). Kidneys accepted pre-KAS and post-KAS had similar KDPI (median 13.0 pre-KAS vs 13.2 post-KAS, p=0.4) (Figure 2, Table 4A).

Pre-KAS, kidneys from 2,296 donors were ever declined on behalf of pediatric candidates, and post-KAS 2,421 were ever declined. Kidneys declined post-KAS were less likely to be from donors <18 years old (22.6% pre-KAS vs 12.1% post-KAS), and more likely to be PHS increased infectious risk (23.4% pre-KAS vs 33.4% post-KAS, p<0.001). Median KDPI of declined kidneys decreased from 25.6 pre-KAS to 20.6 post-KAS (p<0.001) (Table 4B).

Subgroup analysis among pediatric candidates ≤6 years old

Among candidates ≤6 years old, offer rates remained unchanged post-KAS (aIRR: $_{0.90}1.03_{1.17}$, p=0.7). Similar to our main findings, changes in offer rate varied by donor age and KDPI. Offer rates of

kidneys from donors <18 years old with KDPI<35% remained largely unchanged (aIRR: $_{0.70}0.88_{1.10}$, p=0.3) and those with KDPI≥35% decreased (aIRR: $_{0.15}0.22_{0.68}$, p<0.001). Offer rates of kidneys from donors 18-34 years old with KDPI<35% remained unchanged (aIRR: $_{0.96}1.11_{1.29}$, p=0.2), and those with KDPI≥35% decreased (aIRR: $_{0.15}0.21_{0.29}$, p<0.001). Offer rates for kidneys from donors 35+ years old with KDPI<35% increased (aIRR: $_{6.57}9.98_{15.14}$, p<0.001), and those with KDPI≥35% increased (aIRR: $_{1.08}1.52_{2.12}$, p=0.02). Overall acceptance of offers among candidates ≤6 decreased from 10.6% pre-KAS to 7.9% post-KAS (205 vs 185 acceptances), although this was not statistically significant (aOR: $_{0.45}0.73_{1.18}$, p=0.2). Acceptance of kidneys from donors <18 years old with KDPI<35% decreased from 17.0% to 15.9% (aOR: $_{0.40}0.81_{1.62}$, p=0.5) and acceptance of those with KDPI≥35% decreased from 7.0% to 0% (no calculable aOR). Acceptance of kidneys from donors 18-34 years old with KDPI<35% decreased from 11.7% to 8.1% (aOR: $_{0.38}0.66_{1.12}$, p=0.1), and acceptance of those with KDPI≥35% remained unchanged from 5.7% to 5.9% post-KAS (aOR: $_{0.13}0.59_{2.67}$, p=0.5). Finally, acceptance of kidneys from donors >35 years old with KDPI<35% increased from 0% to 5.0% post-KAS (no calculable aOR), and acceptance of those with KDPI≥35% increased from 0% to 2.2% post-KAS (no calculable aOR).

Increased risk for disease transmission (IRD) donors

To understand what might be driving the decreased acceptance among donors 18-34 years old with KDPI<35%, we compared IRD donor offer and acceptances pre- and post-KAS within this donor population. Among donors 18-34 years old with KDPI<35%, total offers from IRD donors increased from 1,484 pre-KAS to 2,818 post-KAS, and the total offers from non-IRD donors increased from 3,200 to 3,822. While offer acceptance of IRD donors 18-34 years old with KDPI<35% remained constant at 3.8% pre-KAS as 4.0% post-KAS (p=0.5), acceptance of non-IRD donors 18-34 years old with KDPI<35% decreased from 19.0% pre-KAS to 15.2% post-KAS (p=0.003).

DISCUSSION

In this national study of kidney offers before and after KAS, we found that KAS significantly altered the types of kidneys being offered to pediatric DDKT candidates. The overall offer rate per person-year increased post-KAS by 13%, from 7.5 offers per person-year to 9.0 offers per person-year. The post-KAS changes in kidney offers were consistent with what might be expected from prioritization changes: post-KAS candidates were 79% less likely to receive offers for kidneys from both donors <18 years old and 18-34 years old with KDPI≥35%, and more likely to receive offers for donors 18-34 years old with KDPI<35%. However, we also found that offer acceptance practices changed post-KAS. Notably, kidneys from donors 18-34 years old with KDPI<35% were 23% less likely to be accepted post-KAS compared to pre-KAS, and kidneys from donors 35+ years old with KDPI<35% were nearly 3-fold more likely to be accepted post-KAS. Our findings indicate that any changes in DDKT rates for pediatric candidates are likely the result of both policy change and transplant community acceptance practices.

While KAS has led to increased transplant rates for the highly sensitized, racial minorities, and certain blood types in the adult population,[3, 13, 14, 50] reports of the impact of KAS on the pediatric population have been mixed.[15-17, 72] Notably, concern over decreased DDKT rates for certain pediatric candidates (particularly for candidates ≤6 years old) has led some to suggest that this is the direct result of KAS – that the policy is at fault – and that modifications to KAS should be considered.[18, 19] These concerns prompted us to analyze changes in offer and acceptance patterns for pediatric candidates after KAS, since changes in these patterns could plausibly lead to changes in DDKT rates. Our findings only partially support the position that KAS is responsible for any changes in DDKT rates. As might be expected from the policy change, post-KAS candidates were 79% less likely to receive offers for kidneys from both donors <18 years old and 18-34 years old with KDPI≥35%, and more likely to receive offers for donors 18-34 years old and 35+ years old with KDPI<35%.

However, beyond the direct consequences of policy change (i.e. changes in offer patterns), we also found evidence that the transplant's community behavior changed (i.e. changes in acceptance patterns). Encouragingly, kidneys from donors 35+ years old with KDPI<35% were nearly 3-fold more likely to be accepted post-KAS compared to pre-KAS, which might reflect an understanding that low KDPI kidneys (even from older donors) could possibly be used with great outcomes in pediatric recipients, although pediatric recipients were not included when creating the KDPI.[75] However, kidneys from donors 18-34 years old with KDPI<35% were 23% less likely to be accepted post-KAS, even after adjusting for donor and recipient characteristics. This might be a consequence of increased selectivity of these high-quality kidneys, since these kidneys were actually 20% more likely to be offered to post-KAS pediatric candidates. This acceptance decrease does not appear to be driven by IRD donors, as acceptance of these offers from IRD donors remained unchanged, albeit low, despite the reasonable safety profile reported thus far.[76-78] Thus, policy change and transplant community behavior might both be contributing to any decrease in DDKT rates for pediatric candidates, and one potential mechanism to mitigate this might be to utilize kidneys from donors 18-34 years old with KDPI<35% post-KAS to the same extent that they were being used pre-KAS.

One limitation of our study is that we were unable to determine the reasons that candidates declined a kidney. For example, candidates might decline a high quality deceased donor kidney if they have a potential living donor in evaluation, and thus the decline does not reflect perceived kidney quality but rather the availability of a potentially better transplant. However, we do not expect rates of living donation to have changed substantially during the relatively short four-year study period, and therefore this should not bias our results, since the effect of this would be similar in both the pre-KAS and post-KAS era. Despite this limitation, we studied full national organ offer data, and so our findings reflect national practice.

In conclusion, the goal of our study was to determine whether reduced DDKT rates for certain pediatric candidates was due to changes in offers to pediatric candidates (i.e. an effect of policy change) or to changes in acceptance practices (i.e. an effect of transplant community behavior). We found evidence of both – while changes in offers largely mirrored what might be expected from KAS prioritization changes, the acceptance of kidneys from donors 18-34 years old with KDPI<35% decreased, and acceptance of kidneys from donors 35+ years old with KDPI<35% significantly increased, post-KAS, indicating that the transplant community's acceptance patterns have changed as well. Using these high-quality kidneys from donors 18-34 years old with KDPI<35% post-KAS to the same extent they were used pre-KAS might be an effective strategy to mitigate any decrease in DDKT rates for pediatric DDKT candidates.

Table 1. Characteristics of pediatric candidates active on the kidney transplant waitlist in the two years pre- and post-KAS

Factor	Pre-KAS (N=2151)	Post-KAS (N=2088)	p-value
Age at entry, median (IQR)	13 (8, 16)	13 (8, 16)	0.9
Age categories, %			0.6
0-6yrs	21.2%	20.1%	
7-12yrs	23.2%	24.5%	
13-17yrs	48.0%	47.3%	
>17yrs	7.6%	8.1%	
Male sex	59.0%	58.1%	0.5
Race			0.2
White/Caucasian	47.1%	48.7%	
Black/African American	25.4%	22.9%	
Hispanic/Latino/Other	27.5%	28.4%	
Time on dialysis, median (IQR)	1.5 (0.6, 3.0)	1.5 (0.7, 3.0)	0.9
Preemptive listing, %	31.2%	29.6%	0.3
Calculated panel reactive antibody, med (IQR)	0 (0, 29.5)	0 (0, 23.6)	0.8

Table 2. Crude offer rate per waitlist-year pre- and post-KAS and adjusted change in offer rate post-KAS among pediatric candidates who accumulated active time on the waitlist in the two years pre- and post-KAS

	Pre-KAS offer rate per waitlist-year[a]	Post-KAS offer rate per waitlist-year[a]	Change in offer rate post-KAS (aIRR)[c]	P-value
All kidneys	7.48 (7.32-7.65)[b]	8.95(8.78-9.13)	$_{1.01}1.08_{1.15}$	0.02
Donor <18yo; KDPI<35%	0.81 (0.75-0.86)	0.82 (0.77-0.87)	$_{0.78}0.88_{0.996}$	0.04
Donor <18yo; KDPI≥35%	0.95 (0.89-1.01)	0.22 (0.19-0.24)	$_{0.18}0.21_{0.25}$	<0.001
Donor 18-34yo; KDPI<35%	4.25 (4.13-4.38)	5.97 (5.83-6.12)	$_{1.12}1.20_{1.29}$	<0.001
Donor 18-34yo; KDPI≥35%	0.88 (0.83-0.94)	0.19 (0.17-0.22)	$_{0.17}0.21_{0.25}$	<0.001
Donor ≥35yo; KDPI<35%	0.12 (0.10-0.15)	1.16 (1.10-1.23)	$_{7.09}8.57_{10.37}$	<0.001
Donor ≥35yo; KDPI≥35%	0.39 (0.36-0.43)	0.59 (0.55-0.64)	$_{1.21}1.43_{1.69}$	<0.001

[a]Pre- and post-KAS offer rate per waitlist-year calculated as the total number of offers made to pediatric candidates of each kidney type divided by the accumulated active waitlist years of pediatric candidates

[b]Interpreted as actively listed pediatric candidates received a mean of 7.28 offers per waitlist year pre-KAS vs 8.95 offers per waitlist year post-KAS

[c]Change in offer rate associated with KAS determined using negative binomial regression with adjustment for candidate age, sex, race, weight, primary diagnosis, time on dialysis, preemptive listing, and cPRA

Table 3. Crude offer acceptance and adjusted relative change in offer acceptance post-KAS among pediatric candidates who were ever offered a deceased donor kidney in the two years pre- and post-KAS

	Pre-KAS acceptance, % (N transplants)	Post-KAS acceptance, % (N transplants)	Change post-KAS (aOR)[a]	P-value
All offers	12.2% (1002)	10.6% (1053)	$_{0.76}0.95_{1.18}$	0.6
Donor <18 yo; KDPI<35%	21.8% (206)	22.1% (201)	$_{0.77}1.06_{1.45}$	0.8
Donor <18 yo; KDPI≥35%	5.4% (58)	3.8% (9)	$_{0.30}0.65_{1.40}$	0.2
Donor 18-34 yo; KDPI<35%	14.2% (665)	10.4% (693)	$_{0.61}0.77_{0.98}$	0.03
Donor 18-34 yo; KDPI≥35%	5.9% (57)	8.6% (18)	$_{0.57}1.07_{2.01}$	0.8
Donor ≥35 yo; KDPI<35%	4.4% (6)	8.4% (108)	$_{1.16}2.82_{6.87}$	0.02
Donor ≥35 yo; KDPI≥35%	2.3% (10)	3.6% (24)	$_{0.75}1.68_{3.74}$	0.2

[a]Change post-KAS estimated using multilevel logistic regression adjusted for candidate age, sex, race, preemptive listing, dialysis time, cPRA, indication for transplant, and secular trends

Table 4a. Characteristics of deceased donor kidneys ever accepted by pediatric candidates pre- and post-KAS

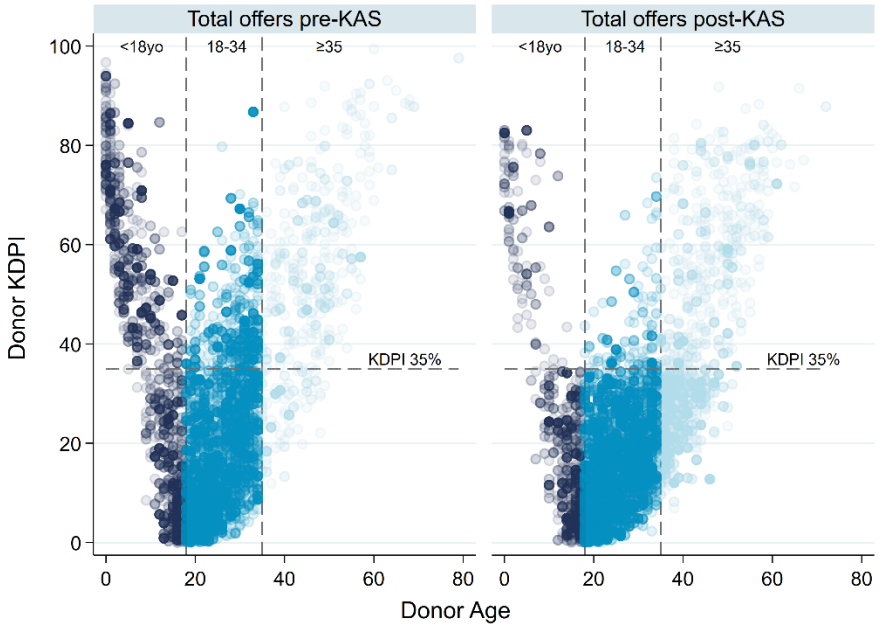
For all candidates	Pre-KAS (N=878)	Post-KAS (N=884)	p-value
Donor Age, median (IQR)	22 (17, 28)	23 (19, 30)	<0.001
Donor Age, categories			<0.001
<18	26.2%	19.6%	
18-24	36.6%	36.9%	
25-34	35.4%	30.3%	
35-50	1.8%	12.7%	
>50	0.0%	0.6%	
KDPI, median % (IQR)	13.0 (6.1, 25.2)	13.2 (6.1, 22.8)	0.4
IRD	8.0%	13.6%	<0.001
DCD	5.5%	4.4%	0.2
Donor cause of death			0.3
Anoxia	25.2%	26.6%	
Stroke	10.2%	8.6%	
Head trauma	61.9%	63.1%	
Tumor/other	2.7%	17%	

Table 4b. Characteristics of deceased donor kidneys ever declined by pediatric candidates pre- and post-KAS

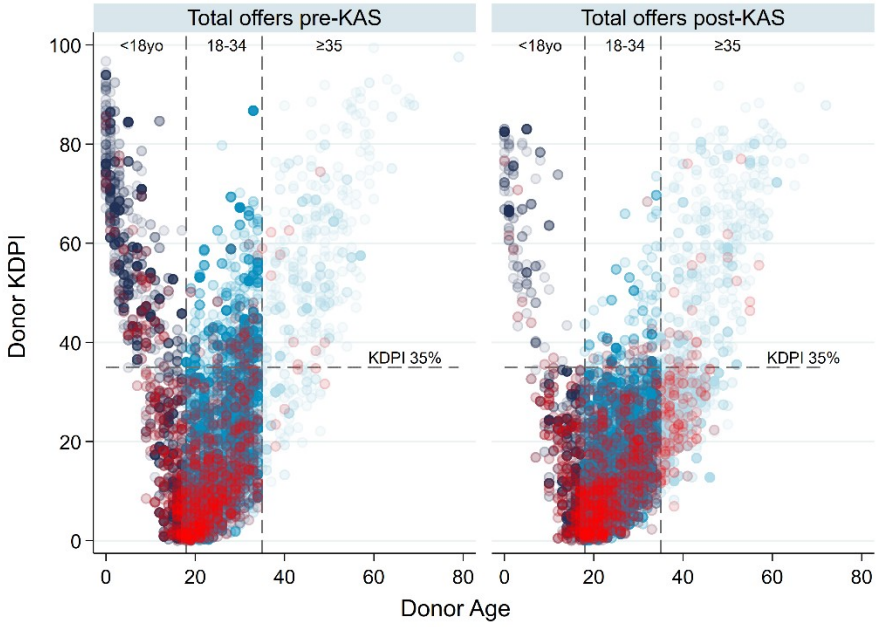
For all candidates	Pre-KAS (N=2,296)	Post-KAS (N=2,421)	p-value
Donor Age, median (IQR)	25 (18,31)	27 (21,35)	<0.001
Donor Age, categories			<0.001
<18	22.6%	12.1%	
18-24	27.4%	29.2%	
25-35	35.8%	32.7%	
36-50	10.8%	21.6%	
>50	3.5%	4.4%	
KDPI, median % (IQR)	25.6 (11.7, 45.2)	20.6 (11.0, 31.5)	<0.001
IRD	23.4%	33.4%	<0.001
DCD	14.1%	13.1%	0.3
Donor cause of death			0.06
Anoxia	38.5%	42.2%	
Stroke	12.5%	10.9%	
Head trauma	45.3%	43.2%	
Tumor/other	3.7%	3.6%	

Figure 1. Total number of offers made, by donor age and Kidney Donor Profile Index (KDPI)

A) Total offers



B) Total offers; accepted offers shown in red



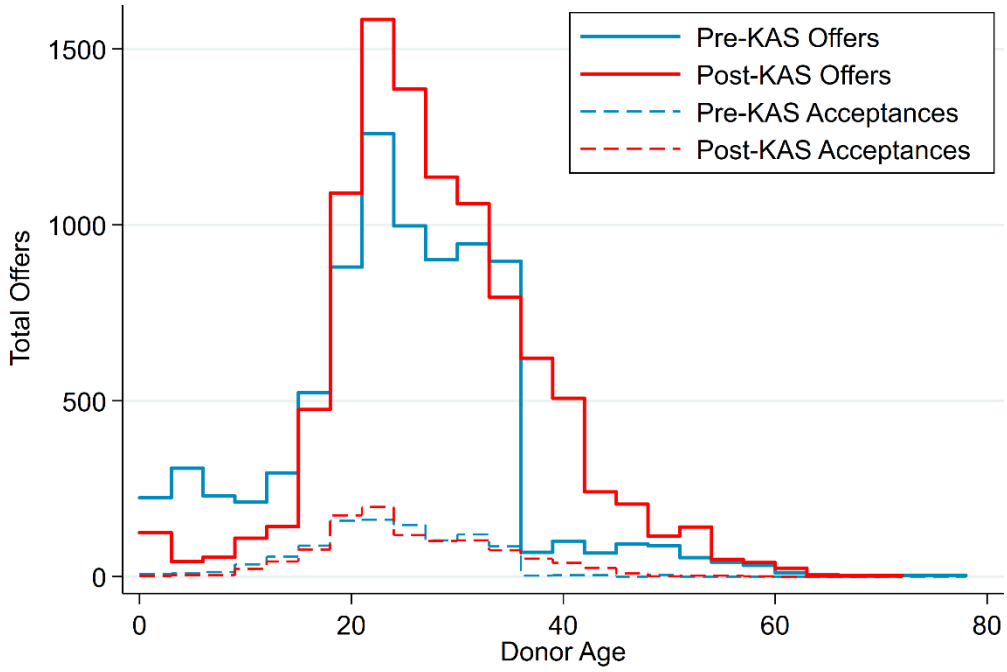
Black = donor <18 years old; blue = donor 18-34 years old; light blue= donor 35+ years old; red = accepted donor. Gray dashed lines delineate donor age and KDPI stratum.

Figure 1A: Overall offers to pediatric candidates increased 13% post-KAS compared to pre-KAS, although this varied by donor age and KDPI stratum. Offer rates decreased for kidneys from donors <18 years old and donors 18-34 years old with a KDPI≥35%. In contrast, offer rates increased for kidneys from donors 18-34 years old with KDPI<35%, and for donors 35+ years old with any KDPI.

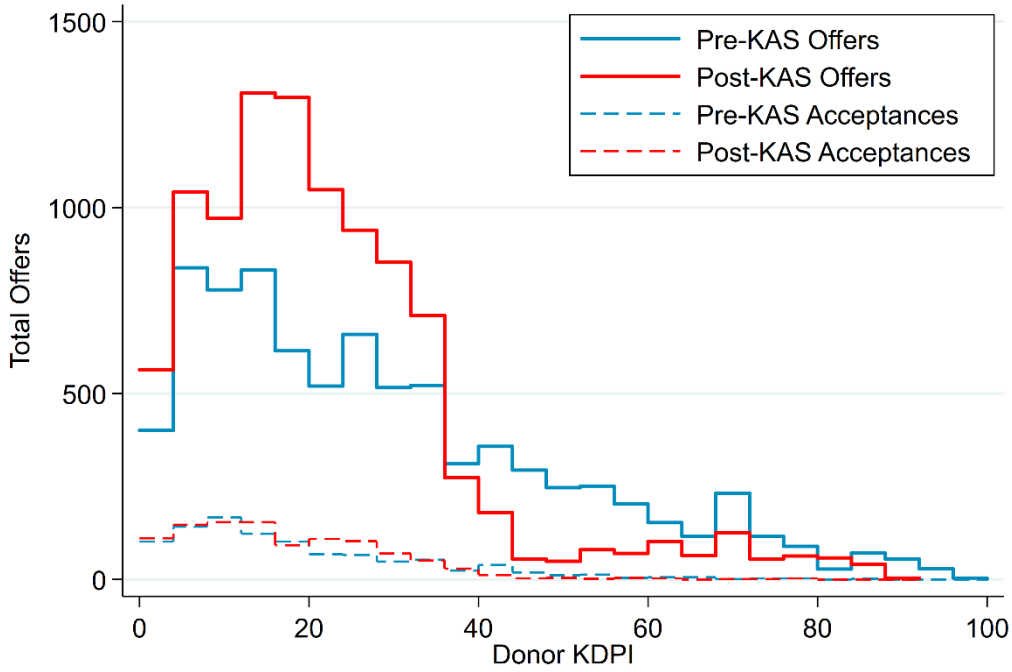
Figure 1B: Overall acceptance for pediatric candidates did not change post-KAS compared to pre-KAS, although this varied by donor and KDPI stratum. The likelihood of acceptance significantly decreased for kidneys from donors 18-34 years olf with KDPI<35%, but actually increased for donors 35+ years old with KDPI<35%.

Figure 2. Distribution of donor age and KDPI of offered (solid lines) and accepted (dashed lines) kidneys pre- and post-KAS. The pre-KAS prioritization of donors less than 35 years old is evident in Figure A, while post-KAS prioritization of donors with KDPI<35% is evident in Figure B. Despite changes in offers, accepted kidneys had similar distributions of donor age and KDPI pre- and post-KAS.

A) Distribution of donor age



B) Distribution of donor KDPI


Pre-KAS Offers
Post-KAS Offers
Pre-KAS Acceptances
Post-KAS Acceptances
Total Offers
1500
1000
500
0
0
20
40
60
80
100
Donor KDPI

Chapter 6. Conclusion

This work has focused on understand how the new Kidney Allocation System (KAS) has impacted two unique transplant populations: highly sensitized (HS) and pediatric (age <18) patients. We used national registry data to quantify post-KAS changes in deceased donor kidney transplant (DDKT) rates for the HS, as well as to understand how these changes led to changing utilization of other transplant modalities. We then used national data to inform potential policy changes to KAS to reverse some unintended consequences for pediatric patients. We characterized post-KAS changes in outcomes after pediatric DDKT, and also post-KAS changes in offer and acceptance patterns.

First, we found that candidates with the highest levels of sensitization had a significantly higher DDKT rate post-KAS (for example, cPRA 98% candidates had a 1.77-fold higher DDKT rate). Moreover, between-cPRA differences in DDKT rates became much smaller, and substantial imbalance only existed between cPRA 99.5-99.9% (3.50-fold higher rate compared to un-sensitized candidates) and 99.9%+ (60% lower rate) candidates. In light of these changes, we also found that HS candidates were 2.25-fold more likely to utilize kidney paired donation but 18% less likely to utilize non-kidney paired donation living donor kidney transplantation in the post-KAS era compared to earlier eras. Thus, KAS has dramatically improved the ability for HS candidates to undergo DDKT, and clinical expansion of kidney-paired donation has allowed for more HS candidates to receive a living donor transplant.

We also found that post-KAS pediatric DDKT recipients had a 41% lower risk of graft loss than pre-KAS recipients, but an equivalent risk of mortality, delayed graft function, and length of stay. We then found that post-KAS candidates were 20% more likely to receive offers from donors age 18-34 with KDPI ≤35%, but were also 24% less likely to accept kidneys from those same high-quality donors. Together, these results indicate that certain unintended consequences of KAS for pediatric

candidates (e.g. a post-KAS decreased DDKT rates for candidates <6 years old) might be the result of transplant community acceptance practices rather than a direct consequence of policy change.

Our results will be used by pediatric and adult nephrologists, transplant surgeons, and policy-makers to understand how KAS has impacted HS and pediatric candidates and recipients to better inform any potential policy changes. Our work provides empiric support for KAS's sliding scale prioritization of HS candidates, although we have identified a select group of the very HS (cPRA 99.5%+) for which substantial imbalance still exists. Any future modifications to KAS to improve equity in DDKT rates for HS candidates might consider this imbalance. Our work also helps inform discussions of potential policy change to KAS for pediatric candidates. We found that transplant community acceptance practices have changed post-KAS, and that any unintended consequences of KAS might not be the direct result of policy change. It is not clear that the current calls for KAS modification would mitigate these unintended consequences, since this would modify policy, not behavior. Nevertheless, ongoing monitoring of waitlisted candidates and transplant recipients should continue, to ensure that the highest-quality data is being used to critically evaluate the impact of KAS on all populations.

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78. Kizilbash, SJ, Rheault, MN, Wang, Q, Vock, DM, Chinnakotla, S, Pruett, T, Chavers, BM: Kidney transplant outcomes associated with the use of increased risk donors in children. *Am J Transplant,* 19**:** 1684-1692, 2019.

CURRICULUM VITAE

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EDUCATION AND TRAINING

Years	Degree	Institution	Discipline
2005-2009	B.S.	University of Texas at Austin	Molecular Biology
2009-2014	M.D.	University of Pittsburgh	Medicine
2014-2017	Junior Residency	Johns Hopkins Hospital	General Surgery
2017-Present	Ph.D.	Johns Hopkins SPH	Clinical Investigation
2020-Present	Senior Residency	Johns Hopkins Hospital	General Surgery

CERTIFICATION AND LICENSURE

Medical licensure:

Years	State
2017-Present	Maryland #D0083255

Professional certifications:

Year	License
2013	Basic Cardiac Life Support (BCLS)
2014	Advanced Cardiac Life Support (ACLS)
2014	Advanced Trauma Life Support (ATLS)
2015	Fundamentals of Laparoscopic Surgery (FLS)
2017	Fundamentals of Endoscopic Surgery (FES)

HONORS AND AWARDS

Year	Award
2009	University of Pittsburgh School of Medicine Dean's Merit Scholar
2009	Phi Beta Kappa
2012	Alpha Omega Alpha (AOA) Medical Honor Society
2012	Doris Duke Clinical Research Fellowship
2012	University of Pittsburgh Clinical Scientist Training Program and Scholarship
2012	Arnold P. Gold Humanism Honor Society
2013	Most Outstanding Senior Student, Department of Surgery, University of

Pittsburgh

2013 Student Surgery Leadership Program, University of Michigan

2017 Ruth L. Kirschstein Postdoctoral Individual National Research Award

2018 American Association for the Study of Liver Diseases (AASLD) Emerging Liver Scholar

2019 American Society of Transplant Surgeons (ASTS) Annual Meeting Poster of Distinction

2019 American Transplant Congress (ATC) Young Investigator Award

2019 American Transplant Congress (ATC) Annual Meeting Poster of Distinction Award

2019 European Society of Organ Transplantation (ESOT) Young Investigator Award

2019 American Association for the Study of Liver Diseases (AASLD) Transplant Surgery Fellow Research Award

RESEARCH ACTIVITIES

Peer-reviewed research articles:

1. Shoemaker-Daly C, **Jackson K**, Yatsu R, Matsumoto Y, Crews D. Genetic Network Underlying Temperature-Dependant Sex Determination Is Endogenously Regulated by Temperature in Isolated Cultured *Trachemys scripta* Gonads. *Dev. Dynam*. 2009; 239(4):1061-1075 [PMID: 20235200]

2. **Jackson KR**, Ruppert K, Shapiro R. Posttransplant Lymphoproliferative Disorder After Pancreas Transplantation: A United Network For Organ Sharing Database Analysis. *Clin Transplant*. 2013; 27:888-894 [PMID: 24118329]

3. **Jackson KR**, Cameron A. Liver transplantation: Candidate selection and organ allocation in the United States. *Internat Anesthsiol Clin*. 2017; 55(2):5-17 [PMID: 28288029]

4. **Jackson KR**, Cameron A. Transplantation of the patient with human immunodeficiency virus. *Adv Surg*. 2017; 51(1):65-76 [PMID: 28797346]

5. Muller X, Marcon F, Sapisochin G, Marquez M, Dondero F, Rayar M, Doyle MMB, Callans L, Li J, Nowak G, Allard M, Jochmans I, **Jackson K**, Beltrame M, van Reeven M, Iesari S, Cucchetti A, Sharma H, Staiger R, Raptis D, Petrowsky H, de Oliveira M, Hernandez-Ajejandro R, Pinna A, Lerut J, Polak W, de Santibanes E, Cameron A, Pirenne J, Cherqui D, Adam R, Ericzon B, Nashan B, Olthoff K, Shaked A, Chapman W, Boudjema K, Soubrane O, Pauam-Burtz C, Greig P, Grant D, Carvalheiro A, Muiesan P, Dutkowski P, Puhan M, Clavien P. Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg*. 2017: 267(3):419-425 [PMID: 28885508]

6. Holscher C, **Jackson K**, Chow E, Thomas A, Haugen C, DiBrito S, Purcell C, Ronin M, Waterman A, Garonzik-Wang J, Massie A, Gentry S, Segev D. Kidney exchange match rates in a large multicenter clearinghouse. *Am J Transplant*. 2018; 18(6):1510-1517 [PMID: 29437286]

7. DiBrito SR, Holscher CM, Haugen CE, Leeds IL, Overton HN, **Jackson KR**, King EA, Haut ER. The modern surgeon scientist. *Ann Surg*, 2018; 268(6):88-89 [PMID: 29629908]

8. Bae S, Massie AB, Thomas AG, Bahn G, Luo X, **Jackson KR**, Ottmann SE, Brennan DC, Desai NM, Coresh J, Segev DL, Garonzik-Wang JM. Who can tolerate a marginal kidney? Predicting survival after deceased-donor kidney transplantation by donor-recipient combination. *Am J Transplant*. 2018; 19(2):425-433 [PMID: 29935051]

9. Holscher CM, **Jackson K**, Thomas AG, Haugen CE, DiBrito SR, Covarrubias K, Gentry SE, Ronin M, Waterman AD, Massie AB, Garonzik Wang J, Segev DL. Temporal Changes in the Composition of a Large Multicenter Kidney Exchange Clearinghouse: Do the Hard-to-Match Accumulate? *Am J Transplant*. 2018; 18(11):2791-2797 [PMID: 30063811]

10. Holscher CM, Ishaque T, Garonzik Wang JM, Haugen CE, DiBrito SR, **Jackson KR**, Muzaale AD, Massie AB, Al Ammary F, Ottman SE, Henderson ML, Segev DL. Living donor post-nephrectomy kidney function and recipient graft loss: a dose-response relationship. *Am J Transplant*. 2018; 18(11):2804-2810 [PMID: 30086198]

11. Holscher CM, Leanza J, Thomas AG, Waldram MM, Haugen CE, **Jackson KR**, Bae S, Massie AB, Segev DL. Anxiety, depression, and regret of donation in living kidney donors. *BMC Nephrol* 2018; 19(1):218 [PMID: 30180815]

12. **Jackson KR**, Covarrubias K, Holscher C, Luo X, Chen J, Massie A, Desai N, Brennan D, Segev D, Garonzik-Wang J. The national landscape of deceased donor kidney transplantation for highly sensitized candidates: transplant rates, waitlist mortality, and post-transplant survival under the Kidney Allocation System. *Am J Transplant*. 2018; 19(4):1129-1138 [PMID: 30372592]

13. Haugen CE, Bowring MG, Holscher CM, **Jackson KR**, Garonzik-Wang J, Cameron AM, Philosophe B, McAdams-DeMarco M, Segev DL. Survival benefit of accepting livers from deceased donor over 70 years old. *Am J Transplant*. 2019; 19(7):2020-2028 [PMID: 30614634]

14. **Jackson KR***, Bowring MG*, Wasik H, Neu A, Garonzik-Wang J, Durand C, Desai N, Massie A, Segev D. Outcomes after declining infectious risk kidney offers for pediatric candidates in the United States. *Transplantation*. 2019; 103(12):2558-2565 [PMID: 30801530] *co-first author

15. **Jackson KR**, Zhou S, Ruck J, Massie AB, Holscher C, Kernodle A, Glorioso J, Motter J, Neu A, Desai N, Segev DL, Garonzik-Wang J. Pediatric deceased donor kidney transplant outcomes under the Kidney Allocation System. *Am J Transplant*. 2019; 19(11):3079-3086 [PMID: 31062464]

16. **Jackson KR**, Long J, Philosophe B, Garonzik-Wang J. Liver transplantation using steatotic grafts. *Clin Liver Dis*. 2019; 14(5):191-195 [PMID: 31879563]

17. Holscher CM, **Jackson KR**, Segev DL. Transplanting the Untransplantable. *Am J Kidney Dis*. 2020; 75(1):114-123 [PMID: 31255336].

18. Holscher CM, Ishaque T, Haugen CE, **Jackson KR**, Garonzik Wang JM, Yu Y, Al Ammary F, Segev DL, Massie AB. Association between living kidney donor post-donation hypertension and recipient graft failure. *Transplantation*. 2019; [epub ahead of print] [PMID: 31335778]

19. Holscher CM, Haugen CE, **Jackson KR**, Garonzik Wang JM, Waldram MM, Bae S, Locke JE, Reed RD, Lentine KL, Gupta G, Weir MR, Friedewald JJ, Verbesey J, Cooper M, Segev DL, Massie AB. Self-reported incident hypertension and long-term kidney function in living kidney donors compared with healthy non-donors. *Clin J Am Soc Nephrol*. 2019; [epub ahead of print] [PMID: 31537534]

20. **Jackson KR**, Holscher C, Motter JD, Desai N, Massie AB, Garonzik-Wang J, Alachkar N, Segev DL. Post-transplant outcomes for cPRA-100% recipients under the new Kidney Allocation System. *Transplantation*. 2019; [epub ahead of print] [PMID: 31577673]

21. **Jackson KR**, Motter JD, Haugen CE, Holscher C, Long JJ, Massie AB, Philosophe B, Cameron AM, Garonzik-Wang J, Segev DL. Temporal trends in utilization and outcomes of steatotic donor livers in the United States. *Am J Transplant*. 2019; [epub ahead of print] [PMID: 31608587]

22. **Jackson KR,** Motter JD, Haugen CE, Long JJ, King E, Philosophe B, Massie AB, Cameron AM, Garonzik-Wang J, Segev DL. Minimizing risks of liver transplantation with steatotic donor livers by preferred recipient matching. *Transplantation*. 2019 [epub ahead of print] [PMID: 31815903]

23. **Jackson KR**, Bowring MG, Holscher C, Haugen CE, Long JJ, Liyange L, Massie AB, Ottmann S, Philosophe B, Cameron A, Segev DL, Garonzik-Wang J. Outcomes after declining a steatotic donor liver for liver transplant candidates in the United States. *Transplantation*. 2019 [epub ahead of print] [PMID: 31815898]

24. Bae S, Garonzik Wang JM, Massie AB, **Jackson KR**, McAdams-DeMarco MA, Brennan DC, Lentine KL, Coresh J, Segev DL. Early steroid withdrawal in deceased-donor kidney transplant recipients with delayed graft function. *J Am Soc Nephrol*. 2019; [epub ahead of print] [PMID: 31852720]

25. Messner F, Etra JW, Yu Y, Massie AB, **Jackson KR**, Brandacher G, Schneeberger S, Margreiter C, Segev DL. Outcomes of simultaneous pancreas and kidney transplantation based on donor resuscitation. *Am J Transplant*. 2020; [accepted for publication; in press]

26. **Jackson KR**, Munivenkatappa RB, Wesson RN, Garonzik-Wang JM, Massie AB, Philosophe B. What's the score? A comparison of deceased donor kidney scoring systems and correlation with graft outcome. *Clin Transplant*. 2020; [accepted for publication; in press]

27. **Jackson KR**, Motter JD, Kernodle A, Desai N, Thomas AG, Massie AB, Garonzik-Wang JM, Segev DL. How do highly sensitized patients get kidney transplants? Trends over the last decade. *Am J Transplant*. 2020; [accepted for publication; in press]

28. **Jackson KR**, Bowring MG, Kernodle A, Boyarsky B, Desai N, Charnaya O, Garonzik-Wang JM, Massie AB, Segev DL. Changes in offer and acceptance patterns for pediatric

kidney transplant candidates under the new Kidney Allocation System. *Am J Transplant*. 2020; [accepted for publication; in press]

Funding, current:

07/2017-06/2020. NIH - F32 DK113719 (PI: Jackson)
Total award: $231,234
Differential survival benefit of incompatible living donor kidney transplantation: modeling outcomes for different patient phenotypes

Funding, previous:

06/2010-07/2010. University of Pittsburgh Dean's Summer Research Grant (PI: Jackson)
Total award: $3,000
Multicenter Analysis of Outcomes of Liver Transplantation in the Infant

07/2012 - 06/2013. Doris Duke Clinical Research Fellowship (PI: Jackson)
Total award, $61,410
Persistent Right Ventricular Dysfunction After Left Ventricular Assist Device Implantation

Poster presentations

1. **Jackson KR**, Spada M, Mazariegos G. Multicenter Analysis of Liver Transplantation in the Infant. University of Pittsburgh School of Medicine Dean's Summer Research Poster Session. Pittsburgh, PA, 2010.

2. **Jackson KR**, McAnaney C, Teuteberg J, Dew MA, Bhama J, Bermudez C, Ramani R, McNamara D, Kormos RL. Early Adverse Events Predict 1-Year Mortality In Patients Supported by Continuous-Flow Ventricular Assist Devices. Doris Duke Clinical Research Fellowship National Meeting. Washington, DC, 2013

3. **Jackson KR**, McAnaney C, Teuteberg J, Dew MA, Bhama J, Bermudez C, Ramani R, McNamara D, Kormos RL. Impact of Early Adverse Events On Later Mortality In Patients Supported by Continuous-Flow Ventricular Assist Devices. International Society of Heart and Lung Transplantation Annual Meeting. Montreal, Quebec, Canada, 2013

4. **Jackson KR**, Luo X, Garonzik-Wang J, Segev D. Incompatible Living Donor Kidney Transplantation Is an Effective Technique for Patients Facing Re-transplantation. American Society of Transplant Surgeons Winter Symposium, Miami, FL, 2018.

5. **Jackson KR**, Covarrubias K, Luo X, Segev D, Garonzik-Wang J. A step towards equality: transplant rates for the highly sensitized under the Kidney Allocation System. Johns Hopkins Department of Surgery Research Day, Baltimore, MD 2018

6. **Jackson KR**, Covarrubias K, Luo X, Segev D, Garonzik-Wang J. A step towards equality? Transplant rates for the highly sensitized under the Kidney Allocation System. American Society of Transplant Surgeons Winter Symposium, Miami, FL, 2019

7. **Jackson KR**, Bowring MG, Massie AB, Segev DL. Survival benefit of liver transplantation with a steatotic donor liver. American Transplant Congress. Boston, MA. 2019

8. **Jackson KR**, Motter JD, Massie AB, Segev DL. How do the highly sensitized get kidney transplants in the United States? Trends over the last decade. American Society of Nephrology Kidney Week. Washington, DC. 2019.

9. **Jackson KR**, Motter JD, Philosophe B, Garonzik-Wang J, Cameron AM, Segev DL. Temporal trends in utilization and outcomes of steatotic donor livers in the United States. The Liver Meeting. Boston, MA. 2019.

10. **Jackson KR**, Bowring MG, Holscher C, Haugen CE, Long JJ, Liyange L, Massie AB, Ottmann S, Philosophe B, Cameron A, Segev DL, Garonzik-Wang J. Outcomes after declining a steatotic donor liver for liver transplant candidates in the United States. American Society of Transplant Surgeons Winter Symposium, Miami, FL, 2020

11. **Jackson KR**, Motter JD, Massie AB, Philosophe B, Cameron AM, Garonzik-Wang J, Segev DL Who can tolerate a DCD liver? Minimizing risks of liver transplantation using DCD livers by preferred recipient matching. American Society of Transplant Surgeons Winter Symposium, Miami, FL, 2020

12. **Jackson KR**, Motter JD, Haugen CE, Holscher C, Long JJ, Massie AB, Philosophe B, Cameron AM, Garonzik-Wang J, Segev DL. How are steatotic donor livers being used for liver transplant in the United States? Trends over the last decade. American Society of Transplant Surgeons Winter Symposium, Miami, FL, 2020

SPEAKING ACTIVITIES

Abstract-based presentations (oral)

National:

1. Pediatric deceased donor kidney transplantation under the new Kidney Allocation System. Academic Surgical Congress, Houston TX, February 2019.

2. Survival benefit of deceased donor kidney transplantation for recipients with a long dialysis vintage. Academic Surgical Congress, Houston TX, February 2019

3. Center-level variation in outcomes following incompatible living donor kidney transplantation. American Transplant Congress, Boston MA, June 2019

4. Minimizing risks of liver transplantation with steatotic livers by preferred recipient matching. American College of Surgeons Clinical Congress, San Francisco CA, October 2019

5. Decreasing risks of kidney transplantation using high Kidney Donor Profile Index kidneys through preferred recipient matching, American Society of Nephrology Kidney Week, Washington DC, November 2019

6. Who can tolerate a DCD liver? Minimizing risks of liver transplantation using DCD livers by preferred recipient matching. The Liver Meeting, Boston MA, November 2019

7. Quantifying the impact of an infection on mortality and graft loss following kidney transplantation. American Society of Transplant Surgeons Winter Symposium, Miami FL, January 2020

8. How do the highly sensitized get kidney transplants in the United States? Trends over the last decade. Academic Surgical Congress, Orlando FL, February 2020 **[upcoming]**

9. Characterizing the landscape and impact of post-kidney transplant infections. Academic Surgical Congress, Orlando FL, February 2020 **[upcoming]**

International:

10. Liver transplant candidates derive a survival benefit from accepting a macrosteatotic liver. International Liver Transplant Society Annual Meeting, Toronto, Canada, May 2019

11. Minimizing risks of liver transplantation with steatotic donor livers by matching to preferred recipients. European Society Of Transplantation Annual Meeting, Copenhagen, Denmark, September 2019

12. Outcomes after declining a steatotic donor liver for liver transplant candidates in the United States. European Society of Transplantation Annual Meeting, Copenhagen, Denmark, September 2019

13. Decreasing risks of kidney transplantation using high Kidney Donor Profile Index kidneys through preferred recipient matching. International Society of Organ Donation and Procurement. Dubai, UAE, November 2019

14. Temporal trends in utilization and outcomes of steatotic donor livers for liver transplantation in the United States. International Society of Organ Donation and Procurement. Dubai, UAE, November 2019

Invited lectures

15. Research in Medical School, University of Pittsburgh School of Medicine. March 2014

16. Life As a 3rd-year Medical Student, University of Pittsburgh School of Medicine. April 2014

17. Introduction to Clinical Research Ethics, Doris Duke High School Summer Academy. May 2014

18. Medical Biostatistics Review, Johns Hopkins Hospital. January 2017

19. Success in Graduate School, Johns Hopkins Bloomberg School of Public Health. October 2018

20. Kidney Transplantation for the Highly Sensitized Candidate: Modern Options, Transplant Nephrology Monthly Conference, Johns Hopkins Hospital. August 2019

21. Changes to Kidney Transplantation for the Highly Sensitized, HLA Laboratory Monthly Conference, Johns Hopkins Hospital. October 2019.

PROFESSIONAL ACTIVITIES

Membership in professional societies (active)

- American College of Surgeons
- American Society of Transplant Surgeons
- American Society of Nephrology
- Association for Academic Surgery
- International Liver Transplantation Society
- European Society of Organ Transplantation

Leadership in professional organizations

Years	Position
2010-2012	President Surgery Medical Student Interest Group University of Pittsburgh School of Medicine Pittsburgh, PA
2012-2013	President Alpha Omega Alpha (AOA) Medical Honor Society University of Pittsburgh School of Medicine Pittsburgh, PA

Leadership, administrative positions

Years	Position
2020-Present	Administrative Chief Resident General Surgery Residency Johns Hopkins Hospital Baltimore, MD

Committee membership

Years	Position
2019-Present	Member Emerging Liver Scholars Ambassador Program American Association for the Study of Liver Diseases (AASLD)
2019-Present	Member Residency Selection Committee Johns Hopkins Hospital, General Surgery Residency Baltimore, MD

Journal peer-review

- Transplantation Direct, ad-hoc reviewer

Mentoring and advising

Years	Activity
2010-2011	Faculty and Students Together (FAST) Program Mentor University of Pittsburgh School of Medicine Pittsburgh, PA
2010-2014	Medical Siblings Program Mentor University of Pittsburgh School of Medicine Pittsburgh, PA
2015-2016	Medical Siblings Program Mentor Johns Hopkins Hospital Baltimore, MD

EDUCATIONAL ACTIVITIES

Educational publications

Book chapters:

1. **Jackson K**, Cameron A. Biliary reconstruction for liver transplantation in patients with primary sclerosing cholangitis: choledochocholedocostomy vs Roux-en-Y hepaticojejunostomy, In: Hepato-Pancreato-Biliary and Transplant Surgery: Practical Management of Dilemmas. Chu Q, Vollmer C, Zibari G, Orloff S, Williams M, Gimenez M. Beaux Books Publishing, 2018, edition 1, Chapter 18

2. **Jackson K**, Philosophe B, Cameron A. Pediatric issues: split liver and living donor liver transplantation, In: The Multi-Organ Donor: E-Guide to Selection, Preservation, and Procurement. Higgins R. 2018, edition 2, Chapter 12, Pages 147-156

Teaching activities

Years	Activities
2013-2014	Biostatistics and Epidemiology Instructor High School MERIT Program, Pittsburgh Science and Technology Academy Pittsburgh, PA
2016-Present	Resident Preceptor Intern Surgical Skills Course, Johns Hopkins Hospital Baltimore, MD
2016-Present	Resident Preceptor Physician Assistant Laparotomy Skills Course, Johns Hopkins Hospital Baltimore, MD
2017-Present	Resident Preceptor

Junior Resident Advanced Techniques Skills Course, Johns Hopkins Hospital
Baltimore. MD

Brief Biosketch

Dr. Kyle R. Jackson was born in Houston, Texas, and grew up in the Texas Hill Country in a small town called Bulverde, Texas. He completed his undergraduate studies in molecular biology at the University of Texas at Austin, and matriculated to medical school at the University of Pittsburgh School of Medicine. During medical school, Kyle was awarded a Doris Duke Clinical Research Fellowship to fund a year of research in the Division of Transplant Surgery, where he developed his clinical and scientific interest in the field of abdominal organ transplantation. He then entered general surgery residency at Johns Hopkins Hospital, where he was awarded an F32 from the NIH to fund a PhD through the Graduate Training Program in Clinical Investigation. Kyle is completing this training now, and will return to finish his residency training before pursuing a fellowship in abdominal organ transplantation. He enjoys travelling with his wife Christina Jackson, exploring new foods, and wine.